G. Dallenbach-Hellweg

Histopathology of the Endometrium

English Translation by F. D. Dallenbach

Third Revised and Updated Edition

With 147 Figures and 2 Colored Plates

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Preface to the Third Edition

Although the purpose and scope of this monograph remain unchanged, I have been obliged to revise and rewrite many sections to keep pace with the recent growth in knowledge of endometrial pathology and physiology.

New knowledge emanates from every quarter, engendered by improved methods of study in virtually every subspecialty, by exemplary cooperation between disciplines, and especially by the exchange of ideas internationally. On the other hand, the catalogue of diseases is everchanging. Some, once common, become rare or even disappear. Others suddenly appear, unique and previously unknown. Increased longevity, modern ways of living and new methods of treatment have modified or augmented the clinical and diagnostic problems confronting us. Accordingly, therapy with hormones and intrauterine contraception receive special attention, commensurate with the importance afforded them today. Under the precept "nil nocere," the almost unlimited uses for these agents warrant that their effects be carefully monitored by precise morphological studies, a prerequisite that succeeds only when clinician and pathologist cooperate closely. The sections on procedures for obtaining endometrial tissue, on steroid receptors, on functional disturbances, and on spontaneous abortion have been changed or expanded to incorporate new facts from recent discoveries that now appear significant. Only time, however, will prove their true value. Much of historical interest in the text has been left intact, for "who wants to read into the future, must consult the past" (André Malraux).

To the correspondents and consultants who have contributed valuable suggestions and brought to my notice errors or omissions in the last edition, I gladly acknowledge my hearty thanks. To my daughter, Friederike, I am particularly grateful, for without her help and untiring support I could never have finished this revision so soon. Again, the Springer-Verlag has earned my deep gratitude for its patience, generosity, and skill in preparing this new edition.

Mannheim/Heidelberg, March 1981 GISELA DALLENBACH-HELLWEG

Foreword to the German Edition

During life form changes. From the form seen we can often interpret function. From such correlation *functional morphology* has developed. When applied to the endometrium it means we use histological features existing at the time of biopsy to diagnose functional changes. What we try to detect are the local reactions induced by hormones under control of higher centers. Correlation of form with function succeeds only when the clinician and morphologist work together. Of the many factors that are important, the time of biopsy is decisive, since the target tissues need time before they can react and change in response to the hormonal stimulus. In our interpretations we must always take such reaction-times into account. By using functional morphology as a method of study, we can determine what type of hormonal dysfunction exists, how intense it is, and how it changes with time. More important, we are able to evaluate the biological effects of the hormonal stimuli on the peripheral target tissues with greater accuracy than if we were to measure the hormones biochemically. Although the advantage may shift in favor of biochemical analyses, as our knowledge progresses in the practice of medicine today the morphological change in the target organ remains the basis by which we recognize disease processes and decide how to treat them.

Besides the changes of functional morphology, we must also evaluate other local changes we find in the histological sections, which, from present-day knowledge, may or may not be induced by hormonal stimuli. Whether certain morphological changes in target organs, particularly the precancerous or carcinomatous transformations, may be brought about by excessive hormonal stimulation or may become refractory to such influences, are questions of extreme importance in learning about the biology of these changes.

In gynecology every morphology must be functional morphology, a principle that particularly applies to the interpretation of the endometrium. My associate, Dr. DALLENBACH-HELLWEG, is an authority on the diagnosis of endometrial changes. Brought up in the HAMPERL school where she became familiar with both general and gynecological pathology, she finished her training under A.T. HERTIG in Boston. By coming to a women's hospital she finally found her way to applied gynecological pathology. Consequently, she is in the position to represent the interests of the clinician as well as those of the morphologist. In this monograph she has recorded her vast experience and thorough knowledge of both disciplines. Her book serves as a bridge between clinician and pathologist, its purpose—to facilitate an exchange of information and ideas in both directions. May the conditions prevail to encourage such trade, hopefully leading to collaboration and teamwork between these specialists.

Mannheim, November, 1969 PETER STOLL

Preface to the German Edition

The endometrium differs from all other tissues of the body in that it rhythmically changes its structure and function. For many years the meaning of these changes remained puzzling and obscure. At about the turn of the century some investigators held the physiological fluctuations of the menstrual cycle to be inflammatory changes. Later, when stricter criteria for the pathology of the endometrium were applied, morphologists misinterpreted pathological fluctuations in the cycle either as physiological variations, or they overlooked them entirely. Today as previously the pathologist is often confronted with the dilemma that he is unable to adequately diagnose the endometrium merely from the structural changes. Accordingly, the gynecologist finds the pathological report of little value. In like manner, if the clinical information given the pathologist is incomplete, then he cannot form a clear notion of the clinical problem.

Although the detection of focal lesions of the endometrium is important, of much greater consequence is the recognition of functional (hormonally controlled) variations and their cyclic course, for it is from these that the clinician is guided in deciding what therapy he should use. The ability to detect such functional changes requires not only that the morphologist possess a thorough knowledge of the physiological and pathological anatomy of the endometrium but also that he receive exact information about the patient's menstrual history and have insight into clinical problems. Prerequisites of that kind make it possible to relate morphology with function, a synthesis essential for the optimal diagnosis of the endometrium. Such a correlation is the purpose of this monograph. It attempts to bridge the gap between pathologist and clinician; it is designed for both. Should these pages stimulate the pathologist's interest for clinical problems or aid the clinician in understanding why the pathologist needs clinical information, thus fostering close cooperation between the two, then the book has achieved its purpose.

The numerous photographs depict most of the endometrial variations that one might encounter. I thank the publishers for accepting so many illustrations and particularly for reproducing halftones of such high quality. Although addressed primarily to the practicing pathologist, this book is intended as well for the gynecologist or research pathologist who, it is hoped, will find among its pages stimulating suggestions and information. May the numerous references cited facilitate further study of special problems. The bibliography, albeit comprehensive, is hardly complete. Every effort was made, however, to cull from the boundless wealth of literature precisely those works that have contributed significantly in their time to the solution of a specific problem.

My special thanks go to Professor Dr. med. PETER STOLL for his critical review of my manuscript, for his invaluable suggestions and advice, as well as

for his helpful and understanding support. I am most indebted to Mrs. G. SANKOVIC for her untiring and dedicated devotion in typing the manuscript and in preparing the bibliography. To Miss B. MERKEL I gladly acknowledge my gratitude for reading the manuscript and for her valued support in overcoming technical problems. Again, I express my sincere thanks to the publishers for their care and efficiency in preparing the text and illustrations, and their willingness to fulfill my many requests.

Mannheim/Heidelberg, November, 1969 GISELA DALLENBACH-HELLWEG

Contents

A. Methods of Obtaining, Preparing, and Interpreting the Endometrium . 1

1. Indications for Curettage 1

2. Selection of the Proper Time for Curettage 2

3. Procedures for Obtaining Endometrial Tissue 4

4. Preparation of the Endometrial Specimen 7
   a) Fixation 7
   b) Embedding 9
   c) Orientation 10
   d) Staining 11

5. Components of Curettings and Their Diagnostic Value 15

6. Statistical Analysis of the Histological Results 20

B. The Normal Histology of the Endometrium 22

1. The Individual Structures 22
   a) The Glandular Epithelium 22
   b) The Superficial Epithelium 25
   c) The Stromal Cells 26
   d) The Reticulum Fibers 31
   e) The Ground Substance 35
   f) The Vessels 35
   g) The Nerves 38

2. Histochemical Localization of Enzymes; the Reciprocal Action between Enzymes and Hormones 38

3. Structural Changes Induced in the Endometrium by the Physiological Action of the Ovarian Hormones 41
   a) Molecular Biology of Steroid Hormones 41
   b) Endometrial Steroid Receptors 45
   c) Estrogen 46
   d) Progesterone 47
   e) Relaxin 47

4. Changes in Structures in the Endometrium During Nidation . . . 48

5. The Endometrium before Puberty 50

6. The Normal Menstrual Cycle and Its Possible Variations 50
   a) The Normal Proliferative Phase 53
   b) The Normal Secretory Phase 58
   c) Menstruation 73

d) Regeneration 80
e) Possible Variations in the Endometrium During the Normal Cycle 80

7. The Endometrium in the Climacterium and after the Menopause . 82

C. The Histopathology of the Endometrium 89

1. Morphological Effects of Circulatory and Coagulation Disturbances 90
a) Edema 90
b) Chronic Passive Hyperemia; Hemorrhage Caused by Extragenital Diseases 92

2. Functional (Hormonal) Disturbances 94
a) Atrophic Endometrium from Non-Functioning Ovaries 95
b) Resting Endometrium Resulting from Inadequate Ovarian Function (Ovarian Insufficiency, Hypofolliculinism) 96
c) The Endometrium Associated with a Persistent Follicle 98
α) The Anovulatory Cycle 98
β) Glandular-Cystic Hyperplasia 102
Adenomatous Hyperplasia 114
γ) Special Forms of Glandular-Cystic Hyperplasia (Focal Hyperplasia, Polyps, Glandular and Stromal Hyperplasias) 123
d) The Deficient Secretory Phase Associated with Premature Regression of the Corpus Luteum 129
e) The Endometrium Associated with Persistent Corpus Luteum . 134
α) Irregular Shedding 134
β) Dymenorrhoea Membranacea 139
f) The Endometrium Associated with Sterility 141
g) Functional Disturbances During the Climacteric 144
h) The Effect of Hormone-Producing Ovarian Tumors on the Endometrium 145
i) The Functional Disturbances of the Endocervical Mucosa . . . 146

3. Endometritis 146
a) Acute Endometritis 147
b) Chronic Nonspecific Endometritis 149
c) Tuberculous Endometritis 151
d) Specific Endometritis Caused by Rare Microorganisms 154
e) The Foreign Body Granuloma 157
f) Endocervicitis 159

4. Neoplasms 159
a) Benign Tumors 159
b) Carcinoma of the Endometrium 161
c) Sarcoma of the Endometrium 199
d) Malignant Mixed Mesodermal Tumors 204
e) Metastatic Tumors 210
f) Primary Carcinomas of the Cervix (Ectocervix and Endocervix) as Components of Curettings 214

5. Iatrogenic Changes of the Endometrium 216
a) After Hormonal Therapy 216
α) Estrogens 217
β) Gestagens 219
γ) Both Hormones 223
δ) Oral Contraceptive Agents 224
ε) Treatment with Gonadotropins 244
b) After Intrauterine Contraceptive Device 247
c) After Intrauterine Instillation 254
d) Regeneration after Curettage 255

D. The Diagnosis of Pregnancy from Curettings 257
1. The Early Intrauterine Pregnancy and Its Disturbances 257
a) Therapeutic Abortion (induced abortion) 257
b) Spontaneous Abortion and Criminal Abortion 259
c) Hydatidiform Mole and Choriocarcinoma 275
2. The Endometrium Associated with Extrauterine Pregnancy 281
3. The Postpartum Endometrium 284

References 290

Subject Index 347

A. Methods of Obtaining, Preparing, and Interpreting the Endometrium

The diagnosis of changes in endometrium obtained by curettage depends not only on a thorough microscopic examination of the histological preparations; the diagnosis actually starts in the clinic. The close interplay between structure and function that is so apparent in the human endometrium requires we ask about or determine what the patient's hormonal state is. We need to know about her menstrual history, previous pregnancies, basal temperature, and any hormones she may have received. What we learn will help us in evaluating the microscopic sections and in detecting abnormal changes.

1. Indications for Curettage

Before a curettage is performed, two questions should be answered: Will the curettage contribute to the diagnosis? What dangers are there in the procedure? Although large statistics indicate the mortality rate for the operation is 0 per cent, in rare instances the uterus may be perforated. On the other hand, with well-founded indications a curettage is especially recommended after the menopause since it often leads to discovery of a carcinoma; or it may also be used to exclude with 100 per cent assurance the presence of such a tumor, thereby sparing the patient a more extensive operation (DAICHMAN and MACKLES, 1966).

Curettage of the endometrium for histological study is indicated:

a) *only rarely*, in conjunction with other methods of study (clinical history, measurement of basal temperature, cytological examination, determinations of hormones), *for diagnosing the functional state when the menstrual cycles are regular*, as for example, in sterility or in trial therapy with hormones. Instead, a simple ("single-stroke" or "strip") endometrial biopsy suffices here and may be carried out in the outpatient clinic or office without dilatation of the cervix.

b) most often *for the diagnosis and treatment of all types of abnormal bleeding*, where the functional (hormonal) or morphological cause needs to be clarified. Here, a complete curettage including the tubal recesses is desirable. To perform it the cervix must be dilated under anesthesia.

c) *when a carcinoma is suspected with or without bleeding;* a complete curettage should be made including the tubal recesses. To insure a thorough and accurate examination the endocervical canal should be curetted separately from the endometrial cavity, and the fragments from each region collected separately. Only enough tissue should be scraped away as is needed for diagnosis if a possibility exists of perforating the uterine wall.

d) in an *abortion* with bleeding and a patent endocervical canal. A complete curettage is indicated here, usually carried out with a large blunt curette. If it can be easily inserted into the endocervical canal, anesthesia is not required.

It becomes apparent that a curettage sometimes serves to supplement or complete a functional diagnosis. At other times, however, curettage becomes necessary as a life-saving procedure. When used for purely diagnostic reasons, then it should be performed at a time optimal for histological study, insuring that the most information will be gained.

2. Selection of the Proper Time for Curettage

The best time depends on the *functional disturbance* presented by the patient and on the diagnosis that the gynecologist anticipates from the histological study. For example, if the clinical signs and symptoms suggest an anovulatory cycle, then a curettage during the proliferative phase would be of little value. A diagnosis of an anovulatory cycle is possible only during the secretory phase, by recognizing that the typical secretory changes have failed to appear in the epithelial cells and stroma. Since the proliferative phase may be prolonged, even normally, and since the first secretion by the glandular cells can be detected with routine stains at best thirty-six to forty-eight hours after ovulation, the curettage should be performed shortly before menstruation. It should certainly be done no earlier than twelve days before the last date for onset of menstruation, as calculated from the clinical history. A diagnosis that ovulation took place can readily be made during the last days of the secretory phase or even on the first day of menstruation, not however directly after ovulation. For most of the other functional diagnoses, particularly for evaluating the function of the corpus luteum and for diagnosing sterility, the late secretory phase is the best and occasionally the only time for curettage to insure a useful histological diagnosis. Admittedly, in patients under study for sterility the danger exists that a pregnancy might be interrupted by curettage in the secretory phase (ARRONET *et al.*, 1973). Such a risk, however, may be circumvented by postponing the curettage until the basal temperature falls; that is, from two days before to just before menstruation starts, provided the basal temperature has been elevated indicating ovulation had probably occurred. In rare instances an endometrial biopsy taken during the "conception cycle" may not disturb the implanting blastocyst and may in fact promote a better decidual reaction (KAROW *et al.*, 1971; ROSENFELD and GARCIA, 1975). Another advantage of curettage in the late secretory phase or just before menstruation, even though the menstrual cycle is irregular, is that the secretory changes should be maximal by then.

Intense hemorrhage but also even *mild atypical bleeding* represent exceptions to the rule of late curettage. Such hemorrhages are an indication for prompt curettage, not only from a clinical standpoint but also from that of the pathologist, since the longer the bleeding continues, the less the amount of tissue to be found in the uterus. Consequently, the chances the histological study will prove worth while diminish with the duration of the hemorrhage. Because of the greater danger of cancer after the menopause, if appropriate clinical signs exist, it is highly advisable to perform a curettage promptly. WINTER (1956) was able to make a pathologic diagnosis in 74 per cent of his patients when the endometrial curettage was performed during the period of abnormal bleeding. When he per-

formed the curettage after the bleeding had ceased, he was able to make a diagnosis in only 34 per cent.

Waiting until bleeding has stopped is justifiable in only a few instances: a) When irregular shedding is suspected. The histological changes typical of that condition are difficult to recognize in curettings obtained on the first day of menstruation. Rather, the histological diagnosis here depends on finding fragments of involuted, though well-preserved endometrium several days after bleeding starts. b) For diagnosing a hypomenorrhea, the curettage is best performed shortly before or three to five days after the onset of menstrual bleeding. If the endometrium is still highly secretory before the bleeding begins, or if only superficial fragments of endometrium are discharged after bleeding has commenced and these reveal involution, then there is no ovarian insufficiency. The changes described more likely represent scanty menstrual shedding with intense shrinkage within normal limits (HINZ, 1953). In rare instances menstrual bleeding fails to occur although ovarian function apparently is normal (PHILIPPE *et al.*, 1966). Since amenorrhea may have various causes, if the endometrium discloses no characteristic changes it is advisable to repeat the curettage; a single strip biopsy suffices.

In summary, the following guide lines (based on HINZ, 1953) are valid:

Clinical diagnosis	*Best time for curettage*
Sterility with suspicion of a corpus luteum insufficiency or an anovulatory cycle:	shortly before or at the onset of menstruation
Hypomenorrhea:	shortly before or three to five days after onset of menstruation
Oligomenorrhea:	on the first day of menstrual bleeding
Menorrhagia with suspicion of irregular shedding:	according to clinical history of bleeding, from five to ten days after onset of menstruation
Amenorrhea (pregnancy must be excluded):	endometrial biopsy repeated at short intervals
Metrorrhagia:	best done without delay

Equally as important as selecting the most favorable time for curettage is the **reporting to the pathologist** about the patient's menstrual history and any hormone therapy she may have received. Besides the patient's name and age, the clinical report sent with the curettings should include: the date of curettage, the date on which the last menstruation started, a schema describing the menstrual cycles, an account of the menstrual flow, details of previous hormonal therapy, a statement about the patient's constitution including any endocrine disturbances, the clinical diagnosis, and questions to be answered (LAU and STOLL, 1963). The pathologist can make an accurate functional diagnosis only if he is sent the pertinent clinical information. For example, it is self-evident why an anovulatory cycle or a shortened or prolonged cycle can be diagnosed only when the phase of the patient's cycle is known, or why secretory change of the endometrium

can be interpreted as deficient only when the day of the cycle is stated. Lack of information about previous therapy with hormones may lead to false interpretations of histological changes and to false conclusions about the patient's ovarian function. Consequently, a purely morphological description of endometrial structure is worthless without correlation with clinical information. Some clinicians maintain that only they are in a position to interpret the histological diagnoses made by the pathologist. I regard such a viewpoint to be wrong. The close interplay between form and function becomes apparent only during the study of a histological preparation, not a posteriori from a histological report. Clinicians and pathologists should endeavor to work together (LETTERER and MASSHOFF, 1941; STOLL 1949; HINZ, 1953; LAU and STOLL, 1963).

3. Procedures for Obtaining Endometrial Tissue

From the pathologist's standpoint it would be ideal to have a *complete curettage* performed lege artis in every patient, since an examination of only all endometrial tissue will insure that no important changes will be overlooked. If the slightest suspicion of carcinoma exists, then the entire endometrial cavity should be curetted. In doing so, it is often advisable to collect the tissue from the corpus separately from that of the endocervical canal, making it possible to localize the tumor. On the other hand, if the purpose of the curettage is to determine the changes brought about by hormonal therapy, that is, to make a functional diagnosis, then a "fractionated" curettage should be employed. Such a study involves repeating an *endometrial biopsy* (strip or single stroke) during a menstrual cycle; it provides more information than a single, complete curettage. In addition, a simple biopsy is usually enough if only a functional diagnosis of the mucosa is sought, for example, in the diagnosis of sterility (SILLO-SEIDL, 1967). Although the amount of tissue obtained with a strip biopsy is relatively scanty, that does not compromise the accuracy of the diagnosis made from it, since the endometrium of the uterine cavity usually develops homogeneously. NOYES (1956) was able to prove that fact by comparing biopsies of the right and left anterior and posterior walls. The decision of what type of procedure to use as well as when to perform the operation will depend upon the patient and the problems involved. If the curettage is indicated for therapeutic reasons, then only a complete curettage will suffice.

Whether a complete curettage is decided upon, or only a biopsy, what is important is that tissue be removed from the endometrial cavity, since all important normal and pathological changes take place in the endometrial cavity, not however (or only very slightly) in the isthmic portion (of the lower uterine segment). A careful curettage of the tubal recesses (cornua) is important, since these are sites of predilection for carcinoma and benign polyps, and they often shelter the last remnants of placental tissue. When the mucosa of the cornua is normal it is particularly high and well-developed, superbly suited for diagnosing functional changes.

In the last few years the histological study of endocervical curettings has become more important for two reasons: 1. Gynecologists have learned the

value of collecting endocervical curettings separately from endometrial curettings, and are practicing the procedure with increasing frequency, especially for the exact localization of a malignancy; 2. therapy with progestational agents, especially certain potent oral contraceptives, induces changes in the endocervix that are characteristic and should be recognized as such.

The Technique of Endometrial Biopsy

The procedure may be carried out in the doctor's office without anesthesia. Preparation: The patient's temperature, leukocyte count and sedimentation rate should be normal. Those with localized or systemic illnesses must be excluded as well as those with a pregnancy as strongly suggested by careful questioning and serological tests. The patient should empty her urinary bladder. After the speculum is inserted and the portio inspected, colposcopy may be done and cytological smears prepared, including wet-mount preparations for phase-contrast microscopy (STOLL, 1970). The uterus is palpated to determine its position and size, attention being paid to adjacent structures.

The portio vaginalis (ectocervix) is cleansed with disinfectants. Under direct inspection and without the need of a tenaculum to stabilize the cervix, the biopsy-curette is inserted into the endocervical canal and up into the fundus. The biopsy of the endometrium is made with a single stroke, usually along the anterior wall, and the curette is withdrawn.

The Technique of Complete Curettage

The procedure is performed best under a brief general anesthesia with an intravenous agent. Preparation of the patient is the same as for the endometrial biopsy (see above). After the pubic hair is trimmed away with scissors, the vulva is cleansed with disinfectants. The portio vaginalis is grasped with a tenaculum and pulled lightly to stretch the uterus. A probe is inserted and the endometrial cavity carefully explored and evaluated. The endocervical canal is then enlarged with Hegar dilators up to size No. 10. A sharp curette is inserted into the endometrial cavity and strips of endometrium gently scraped from the anterior, posterior, right and left uterine walls. The strips of tissue are collected on a linen cloth on the instrument table, examined, and promptly placed in an appropriate fixative. A more thorough curettage may be made by ensuring the strokes of the curette parallel one another and reach the tubal recesses.

When a carcinoma is suspected the endocervix should be scraped first before the curette is inserted into the endometrial cavity; the fragments of endocervical mucosa should be collected separately and fixed. If friable, soft, gray-white tissue is removed from the corpus, highly suggestive of a carcinoma, then the curettage should be discontinued to insure the uterus is not inadvertently perforated by additional scraping.

Emptying the endometrial cavity in an incomplete abortion. If the products of conception have not been discharged it is best to wait until they are spontaneoulsy expelled if the patient's condition permits. Premature intervention requires dilatation of the endocervical canal and the subsequent danger of a cervical insufficiency. In addition, the physician may be accused of having performed an abortion. If the cervical os is found dilated a finger's breadth, permitting insertion of a curette, then no anesthesia is required unless to spare the patient possible psychic trauma. After shaving off the pubic hair, the vulva is cleansed with disinfectants. The urinary bladder is emptied by catheter and the vagina cleansed. The position, size, and consistency of the uterus and neighboring structures are determined by careful palpation. A speculum is inserted and the portio carefully inspected, paying special attention to evidence of disease. The cervix is seized and held fast with a tenaculum and the endometrial cavity explored with the largest blunt curette possible. To stimulate uterine contraction three I.U. of oxytocin are injected i.v. before the curettage is begun. The curettage is performed gently to make sure the soft trophoblastic tissue is removed but not the underlying basal layer of the endometrium or the myometrium. Curettage is completed when the uterus contracts well.

Procedure with a hydatidiform mole. Occasionally with a hydatidiform mole two curettages become necessary, the first being limited to partial removal of the mole to allow the uterus to contract. Later, a second and complete curettage is performed. The procedure used depends on the severity of bleeding. It is advisable to inject oxytocin during the curettage.

Besides biopsing the endometrium with a curette, *biopsy by suction* (vacuum aspiration) can also be used. It has proved ideal for office practice because it is so simple to perform.

For such a suction-biopsy NOVAK (1935, 1937) and RANDALL (1935) employed a thin, hollow probe with a saw-toothed rim. The instrument can be inserted without dilatation of the endocervical canal or anesthesia, and used to detach and aspirate fragments of endometrium from the uterine cavity. NOVAK's probe has subsequently been modified in various ways by numerous other investigators. NUGENT (1963) compiled the results of several series of studies made with the suction-biopsy and calculated that among 1434 biopsies cancer was overlooked in 7.9 per cent (for further literature see NUGENT, 1963). With the probe designed for suction-biopsy by FREISCHÜTZ and JOPP (1964), however, the use of vacuum-suction and sharp excision with a retractable ring-knife within the hollow probe make it possible to remove larger pieces of endometrium. The jet-washer introduced by GRAVLEE in 1969 combines suction with a system for flushing the uterine cavity with physiological saline. The method has proved fairly popular. Since then, further technical improvements have been described and introduced for collecting endometrial tissue suitable for diagnosis (HALE *et al.*, 1976; INGLIS and WEIR, 1976; FERENCZY *et al.*, 1979); their value, however, has not been proved as yet by statistical analyses. Numerous investigators have tested the reliability of many of these methods, especially those used for detecting carcinoma, by comparing the histological diagnoses of them with those made of an ensuing complete curettage or a hysterectomy specimen. When suction biopsy was compared with complete curettage, the histological diagnoses agreed in 81% of the patients (GREENWOOD and WRIGHT, 1979, with 891 patients) or in 96% (KAHLER *et al.*, 1969, with 160 patients; see also DENIS *et al.*, 1973; COHEN *et al.*, 1974; HATHCOCK *et al.*, 1974; MUENZER *et al.*, 1974; LIU *et al.*, 1975; WALTERS *et al.*, 1975; WEBB and GAFFEY, 1976). In contrast, reports indicate agreement with the jet-wash method varies greatly. With that method HENDERSON *et al.* (1975) were able to collect enough tissue for diagnosis in only 58% of their studies but increased the diagnostic accuracy to 92% when they performed simultaneous cytological studies of the perfusion fluid. LUKEMAN (1974) found that agreement in diagnoses for his patients was 89.8%. According to many authors, the diagnostic reliability of the suction and jet-wash methods is equally good (DOWLING *et al.*, 1969; SO-BOSITA *et al.*, 1970; HIBBARD and SCHWINN, 1971; KANBOUR *et al.*, 1974; RODRIGUEZ *et al.*, 1974). Generally the suction biopsy is recommended for patients who are in poor general health or are anesthetic risks (HALLER *et al.*, 1973), and for functional diagnoses in young women (ENGELER *et al.*, 1972; MATHEWS *et al.*, 1973).

From our experience the diagnostic value of the tissue obtained either by suction or by jet-washing depends primarily on the amount of intact tissue that can be collected. Because the interrelationships between gland and stroma are so important in evaluating the quality of neoplastic and preneoplastic hyperplasias, without these interrelationships important distinctions cannot be made. Consequently, we prefer the suction method to the pure washing methods (cf. also VASSILAKOS *et al.*, 1975). For diagnosing endometrial *function,* the strip or suction biopsy is adequate in most instances and well recommended as a method that saves time and expense (see alo ANSARI and COWDREY, 1974). Although a complete curettage performed afterwards may at times contain polyps which escaped the suction biopsy, these contribute no information needed for the functional diagnosis.

Despite all the encouraging reports about the diagnostic reliability of detecting endometrial cancer by suction biopsy, a warning should be issued against placing too much reliance on that method. As a method, it has the same limitations as does endometrial strip-biopsy with the curette. Certainly under optimal conditions a carcinoma may be diagnosed with both methods. Failure

to find carcinoma in the tissue removed with these two methods, however, does not prove that there is no carcinoma in other parts of the endometrium. That holds true especially for the early stages, since endometrial carcinoma generally develops in the basalis or in tubal recesses which are difficult to reach by suction.

For purposes of thoroughness we should mention the use of *whole uteri* in the study and diagnosis of the endometrium. For the pathologist, whole uteri represent ideal specimens for study. When properly examined, they present no problems in diagnosis, nor do they require such detailed diagnoses as do curettings, except when a carcinoma is present.

Besides providing tissue for histological studies, freshly extirpated uteri are a source of material for *cytological smears* and tissue culture. Desquamated, viable epithelial and stromal cells may be examined in wet-mount preparations under the phase-contrast microscope, or in fixed smears stained after the Papanicolaou method or other techniques (SCHÜLLER, 1961; DALLENBACH-HELLWEG and JÄGER, 1969). In some respects the study of living cells with phase-contrast yields information that histological sections cannot provide; for example, knowledge about ciliary motion of the columnar epithelium, or about motility of bacteria or protozoa.

Cytological studies alone are unsuitable for evaluating endometrial function or for diagnosing carcinomas. They fail to provide the cellular interrelationships of the tissue so important for making a definitive diagnosis. Since the study of material obtained by sponge and brush techniques is based on cytologic criteria, these techniques have proved unsatisfactory. The "strip" or suction biopsy are preferred, particularly because they are easiest for patient and physician.

4. Preparation of the Endometrial Specimen

a) Fixation

Since the endometrium is exceedingly soft and undergoes rapid autolysis, it should be carefully handled and promptly fixed. Before fixation, however, it is best to remove clots of blood and mucus. These may be separated either by rinsing the fragments of tissue gently in physiological saline or by spreading them on a fine-meshed sieve or fabric, from which they may be transferred into the fixing solution with one arm of a blunt forceps, exercising care to avoid squeezing or pinching them. If the curettings are left in the gauze or tampon for delivery to the pathologist, then subsequent drying and squeezing will make it difficult for the pathologist to remove the now sticky fragments from the meshes of the gauze. Consequently, we recommend that endometrial curettings never be wrapped in fabric.

In selecting a fixative one should be guided by the principle of trying to preserve intravital structures as completely as possible. To obtain the finest preservation, however, it would be best to forgo a fixative entirely, and instead prepare *sections of unfixed, rapidly frozen tissues* with the *cryostat*. Such sections preserve

most structural details, are free from artefacts owing to shrinkage, and provide a fair facsimile of the living state (KERN-BONTKE and WÄCHTER, 1962). Since, however, knowledge in histopathology has been acquired through the use of fixatives and embedding techniques, and since the diagnoses we make depend in part on the artefacts produced in the tissues during its processing, frozen sections free of such artefacts usually are more difficult to interpret. An example of the difficulty one might encounter is the absence in frozen sections of basal vacuoles in the glandular epithelium during the early secretory phase. In preparing paraffin sections the accumulations of glycogen in these cells dissolve away, leaving instead diagnostically important vacuoles behind. In frozen sections, however, the glycogen remains and no prominent vacuoles form. Further, only a few dyes stain frozen tissue at all well; the structures of the tissue usually display much less contrast of color (eosinophilia, basophilia) than they do in fixed tissues. The greatest disadvantage of frozen sections is that to prepare them one needs special equipment generally not found in a routine histological laboratory. The tissues must be rapidly frozen to prevent large ice-crystals from forming. If not sectioned directly, they must be stored at low temperatures until later. Submitting tissue by mail for study virtually precludes frozen sections, which are best used for emergency or rapid diagnoses and for investigative studies, especially for enzyme histochemistry.

Fixatives may be classified into coagulants, which denature the proteins of tissue, and non-coagulants, which stabilize the proteins by chemical bonding (BAKER, 1963). The best known coagulant fixative is *ethyl alcohol.* By extracting water, it induces substantial shrinkage of tissues and cells. It coagulates nuclei and cytoplasm, destroys mitochondria and chromosomes, dissolves lipids or causes them to diffuse. In brief, with alcohol fixation much of the fine structure of the cell is lost.

The most commonly employed non-coagulant is the aqueous solution of formaldehyde (H_2CO), *formalin.* It preserves the hydrophilic groups of proteins, and probably links chains of proteins together by reacting with the $—NH_2$ of the side groups of certain amino acids (BAKER, 1963). The majority of the formaldehyde-protein linkages are reversible by washing the fixed tissue in water. Consequently, proteins are not denaturated, and any shrinkage of tissue that develops is followed by expansion. DNA, mitochondria and the fine structures of cells remain well-preserved. In general, formalin does not dissolve lipids. Although it does not fix soluble carbohydrates, it does impede the solution of glycogen from tissues by fixing the proteins. The ideal concentration for almost all staining methods used in the diagnosis of the endometrium is a 4 per cent neutral solution of formaldehyde (that is, a 10 per cent solution of the strong commercial 40 per cent formalin). For routine use in the clinic and in office practice formalin has the advantage of being inexpensive, easy to handle, and fairly stable, especially when buffered at pH 7.0. We use a buffered solution since the best linkage of formaldehyde to the tissue proteins takes place around pH 7.0–8.0. As the pH of the formalin rises to pH 10 or more the number of protein-formaldehyde linkages falls. Tissue may be left in the fixative for weeks without harm; thus, it is ideal for fixing specimens to be mailed, or suited for storage of excess tissue for long periods if such becomes necessary. Fixation with formalin enables

the pathologist to use almost all important stains that he might need for differentiating tissues, cells and cellular structures. Most cytoplasmic constituents remain well-preserved, except for some enzymes and a small amount of glycogen. Lipids (particularly neutral fats) and some glycogen may be dissolved from the tissue during its dehydration for paraffin embedding. To expedite the fixation and reporting of fresh gynecological tissues sent to our laboratory, we promptly examine and describe the specimens on receipt, select representative portions for study, trim these to no thicker than 3 mm, and fix them in buffered 4 per cent formalin at 70° C for 90 minutes. To prevent formalin precipitates from forming, we wash the tissue samples (now in capsules) in running cold tap-water for at least ten minutes.

Mixtures of fixatives, made by combining two or more primary fixatives, have advantages derived from the good properties of each component as well as from the favorable and unfavorable reactions of the additives with one another. One usually selects a compound fixative for a special purpose; for example, for preserving chromosomes or specific cytoplasmic inclusions. For such purposes the compound fixatives are generally superior to the primary fixatives.

If, in addition to fixation for routine diagnostic work, one wishes to carry out enzyme studies, for example, of acid phosphatase, he may add *calcium chloride* to the formaldehyde solution without fear its fixative properties will be impaired. The formula for such a fixative, as given by BAKER (1946), is: 10 ml of 10 per cent formalin, 10 ml of a 10 per cent aqueous solution of $CaCl_2$, 80 ml of distilled water. Fixation is carried out at 4° C, and to preserve enzyme activity fixation should not be prolonged more than 12–18 hr.

Many other solutions or mixtures, named after the men who invented them (STIEVE, BOUIN, ZENKER, SAN FELICE, CARNOY) fix tissues particularly well, rendering excellent preservation of histological structures and superb retention of nuclear details. These fixatives, however, are more difficult to prepare and they limit the number of staining methods that may be used. Therefore, these mixtures generally are reserved for research studies. All other types of fixatives should be employed only in emergencies when nothing else is available. Thus, as mentioned above, alcohol is unsuitable as a fixative in any concentration since it causes the loose and fluid-rich endometrium to shrinkage, badly distorting most of its structures.

b) Embedding

Although *paraffin* may not be the best *embedding* medium, it is at least good, easy to use, and inexpensive. An alternative medium would be the polyester waxes, which are convenient but at present too expensive. If the techniques of dehydration and embedding are carried out properly, by insuring that the various solutions are replenished frequently and that dehydration is not unduly prolonged, shrinkage of the tissue may be minimized.

To facilitate processing of the specimens we receive each day, we use a mechanical tissue processor (a histological dehydrating-embedding apparatus) that automatically carries the tissue specimens through the following solutions during the night:

80 per cent ethyl alcohol for $^1/_2$ hour.
80 per cent ethyl alcohol for 1 hour.
96 per cent ethyl alcohol—No. 1 for 1 hour.
96 per cent ethyl alcohol—No. 2 for 1 hour.
100 per cent isopropyl alcohol—No. 1 for 2 hours.
100 per cent isopropyl alcohol—No. 2 for 2 hours.
100 per cent isopropyl alcohol—No. 3 for 2 hours.
xylol-isopropyl alcohol 1 : 1 for 1 hour.
xylol—No. 1 for $^1/_2$ hour.
xylol—No. 2 for $^1/_2$ hour.
Paraplast at 60° C—No. 1 for 2 hours.
Paraplast at 60° C—No. 2 for 2 hours.
In the morning the tissues are ready for embedding in Paraplast.

Frozen sections of endometrium are difficult to make. They turn out well only when the tissue is firm, as in some carcinomas or in retained products of conception. In those instances when frozen sections are needed for special stains it is best to select a firm piece of tissue for sectioning. The remaining fragments should be fixed, embedded, and sectioned as usual, since the study of all tissue is important if one wants to avoid overlooking an early carcinoma or small remnants of decidua.

c) Orientation

When possible, the fragments of endometrium should be placed in the paraffin so the mucosal surface is perpendicular to the plane at which the block will be sectioned. If the entire uterus is available then there will be no difficulty in properly orienting the tissue or in selecting specimens from specific regions of the endometrial cavity and numbering them accordingly. Since we generally receive endometrial curettings in small fragments, it is virtually impossible to orient their mucosal surfaces properly. What we must do then is to place as many fragments on the bottom of the paraffin-well as is feasible to insure all are sectioned. Only when curettings are extraordinarily plentiful is it safe to embed only part of them. Abundant curettings usually come from advanced pathologic conditions that are easy to diagnose, as for example, a large endometrial carcinoma, extensive glandular-cystic hyperplasia, or an abortion. Carcinomatous tissue, characteristically yellow-white, firm but crumbly and granular, can usually be recognized grossly by these features. In contrast, fragments of a glandular-cystic hyperplasia are softer, smoother, edematous and consequently translucent. Remnants of a placenta can be distinguished by their sponginess. Inspite of careful blocking and sectioning of the curettings, if a satisfactory diagnosis of them cannot be made, then it is advisable to re-embed the fragments by turning them 90°. The practice of preparing step-sections of curettings, as routinely followed at some institutes, insures a more thorough study of the tissue and affords a better chance for detecting small, localized lesions. The disadvantage of step-sections is that the tissue cut away between them is lost forever. Therefore, we find it advisable to section first at only one level. Then, depending on the case and how unclear or complicated the tissue changes are, we decide whether to re-embed the curettings or to section the block at deeper levels.

d) Staining

For the experienced pathologist the standard *hematoxylin-eosin stain* is adequate for diagnosing all important pathological changes of the endometrium. Since one should endeavor, however, to gain as much information from the occasionally scanty curettings as possible by making not only a pathological diagnosis but a functional diagnosis as well, we find it worthwhile to employ two additional stains routinely. These are the periodic-acid Schiff (PAS) reaction and the van Gieson stain.

The *PAS reaction* (method: ROMEIS, 1968, §§ 1120–1122) is particularly helpful in making functional diagnoses by staining smallest amounts of glycogen or mucus that normally are inapparent with other stains (AUGUSTIN, 1952); with the reaction, finely dispersed droplets of glycogen can be detected in the glandular epithelium as early as the second half of the proliferative phase. Glycogen persisting in the glandular epithelium long after a pregnancy and invisible with hematoxylin-eosin stains may be colored with the PAS reaction, enabling one to diagnose that there had been a pregnancy, although it may have clinically gone unrecognized (CRAMER, 1957). Hyalinized remnants of decidua retained postpartum or postabortum give a positive PAS reaction and therefore can be readily distinguished from the surrounding unstained structures. In contrast, with hematoxylin-eosin the decidual remnants stain like all other parts, making their recognition difficult (ELSTER and SPANKNEBEL, 1959). During the secretory phase if glycogen is found in only some of the glands, that disparity in distribution indicates ovarian function is abnormal. The PAS reaction may also aid one in recognizing and classifying mucoepidermoid carcinomas or mucus-secreting adenocarcinomas, since these tumors at times produce scanty amounts of mucus inconspicuous in sections stained with hematoxylin-eosin.

The *van Gieson stain* (Method: ROMEIS, 1968, § 708) is useful for detecting polyps, for it colors their stroma of delicate collagenous fibers red, making the polyps stand out from the unstained normal endometrial stroma. The van Gieson stain proves particularly helpful in distinguishing polyps when their glands resemble those of the remaining endometrium. Another advantage of the van Gieson stain is its distinctive staining of old placental villi embedded in fibrin. The villi stain bright red, the sheaths of fibrin yellow. In contrast, with the hematoxylin-eosin stain both stain pink, as do other necrotic remnants of tissue, making recognition of the villi difficult.

Because of these advantages we routinely employ the PAS reaction and the van Giesen stain, in addition to the hematoxylin-eosin stain. All are easy to perform on large numbers of sections.

Several other special stains and histochemical reactions have proved worthwhile for clarifying particular defects of the endometrium and for diagnosing functional bleeding and sterility of endometrial origin. These methods should be employed whenever problems in diagnosis arise (STOLL *et al.*, 1954). A few examples of these special stains will be considered here under the discussion of techniques; the reader will find a more detailed account of the uses and advantages of these methods under the discussion of the appropriate pathologic conditions.

Special methods for demonstrating the fibers of connective tissues: The *Masson-trichome stain* (method: ROMEIS, 1968, § 1538) is useful for demonstrating in degenerating decidual cells the socalled "collagen inclusions", which may indicate that a pregnancy had occurred sometime before (DALLENBACH-HELLWEG, 1961). With careful study these inclusions may be recognized even in the van Gieson stain. In sections stained with hematoxylin-eosin they are invisible. The *demonstration of reticulum fibers* (with, for example, the method of GOMORI: ROMEIS, 1968, §§ 1573–1575) may be of diagnostic value in irregular shedding of the endometrium, since in that condition the reticulum fibers fail to undergo normal dissolution in those regions where menstrual shedding is retarded. Occasionally, it is important to demonstrate reticulum fibers when one wishes to differentiate polyps or endometrial tissue from the isthmic region, which is rich in stromal fibers, from the corpus endometrium which is poor in fibers. Further, it is often possible with the reticulum stain to detect that the patient used oral contraceptive agents since the endometrium under that therapy forms almost no fibers (WAIDL *et al.*, 1968). As ELSTER and SPANKNEBEL (1959) have shown, the *Goldner* stain may be used to differentiate the connective tissue fibers (they stain green) from other structures of the stroma (nerve fibers, vessels) that stain pink. With the Goldner stain the stroma of polyps stains bright green, distinguishing them from the gray-green of an atrophic endometrium or from the yellow-brown of the myometrium. Moreover, the Goldner stain is useful in detecting regions that have undergone a hyaline change: the amorphous parts of an incompletely desquamated endometrium stain pale green; the thickened hyalinized walls of capillaries found after an abortion are colored bright green; the hyaline thrombi in a glandular-cystic hyperplasia appear gray-brown; the edematous stroma stains from yellow to red.

Histochemical reactions for demonstrating nucleic acids: In establishing a functional diagnosis it may be important to determine the content of desoxyribonucleic acid (DNA) of the endometrial cells. DNA is stained easily and well with the *Feulgen reaction* (method in ROMEIS, 1968, § 1192ff.). Since the content of ribonucleic acid (RNA) in glandular and stromal cells serves as a measure or criterion of the effect of estrogen, it is often worthwhile to stain for RNA. For that we may use either the *methyl green-pyronin* stain (after PAPPENHEIM-UNNA, ROMEIS, 1968, §§ 1199 and 1200) or the *gallocyanin-chromalum* method (after EINARSON, ROMEIS, § 1203). With the latter, however, both RNA and DNA are stained, requiring that the DNA be removed by digestion with desoxyribonuclease before we apply the method. Because plasma cells contain abundant RNA and are an important sign of chronic inflammation, both the methyl green-pyronin stain and the gallocyanin-chromalum method may be used to good advantage in detecting them.

Special staining reactions based on proteinaceous components of cells: We can demonstrate proteins of cells with the *tetrazonium reaction.* If we benzoylate the sections first before the reaction, then we can reveal histidine, or if we first treat the sections with "H-acid" (Hoechst Co., Germany) then we can restrict our staining to tryptophan and arginine (method: PEARSE, 1968, p. 612). Certain amino acids may be visualized by coupling them to diazo dyes or to similar reagents. For example, the *Millon reaction* has proved of value in detecting

tyrosine (PEARSE, 1968, p. 606); tryptophan can be demonstrated with the DMAB-nitrite method of ADAMS (PEARSE, 1968, p. 615 or ARNOLD, 1968, p. 127); arginine is readily stained with the *Sakaguchi reaction* (PEARSE, 1968, p. 617). The reaction of BARRNETT and SELIGMAN (ARNOLD, 1968, p. 128) is particularly useful for revealing SH-groups. For staining the basic SH-groups we use the *aldehyde-fuchsin reaction* (method after CAMERON and STEELE: HUMASON, 1962, p. 168). Since the reaction also detects SO_3 groups of acid mucopolysaccharides as well as the aldehyde groups of lipids, we must differentiate our results as outlined in Table 1 below:

Table 1. Histochemical differentiation of the chemical groups revealed with the aldehyde-fuchsin reaction

	Aldehyde-fuchsin positive		
	SO_3-groups in acid mucopolysaccharides	SH-groups in basic proteins	aldehyde groups in lipids
Aldehyde-fuchsin without oxidation	+	+	−
Metachromasia	+	−	−

Often the occurrence of countless endometrial granulocytes (differentiated stromal cells) in the second half of the secretory phase gives rise to the erroneous diagnosis of endometritis. In questionable cases the HELLWEG modification (1954) of the *phloxine-tartrazine stain* of LENDRUM (1947), an uncomplicated method for demonstrating protein, may be helpful in proving that the cells present are endometrial granulocytes:

Paraffin sections of formalin-fixed tissue are first stained with hematein or iron-hematoxylin (as nuclear stains). Sections are then washed in tap water until blue, and stained for 30 minutes in the following solution: Phloxine (C.I. 45410) 0.5 g, calcium chloride 0.5 g, distilled water 100 ml. Sections are washed in tap water. To differentiate and counterstain, a saturated solution of Tartrazine (C.I. 19140) in ethylene glycol (Cellosolve) is dropped onto the sections individually until, as checked under the microscope, all phloxine is washed free from the tissue except from the cytoplasmic granules of the endometrial granulocytes. The differentiation usually takes only one minute. The sections are then washed in 60 per cent ethyl alcohol and run up through a series of alcohols of increasing strength to xylene. Sections are mounted with Canada balsam.

In sections stained with hematoxylin-eosin the protein-rich cytoplasmic granules of these modified stromal cells are uncolored and inconspicuous. With the phloxine stain, however, the granules turn bright red and contrast sharply from their surrounding yellow cytoplasm. Since granulocytic leukocytes and lymphocytes possess no such granules, it is easy to distinguish the endometrial granulocytes from them. The phloxine-tartrazine stain is also valuable for revealing hornified epithelial squames from a previous pregnancy or keratinized pearl formations of a carcinoma, as well as for differentiating between muscle fibers (red) and connective tissue (yellow).

Special methods for demonstrating polysaccharides: Both the *PAS reaction* (see above) and the *aldehyde-fuchsin reaction* (see above) are suitable for making

more precise evaluations of ovarian function (STRAUSS, 1963). By means of the distinct, colorful, and contrast-rich staining of the acid mucopolysaccharides we may detect the onset of mucus secretion of the glandular epithelium almost a week before glycogen can be demonstrated. If we use the aldehyde-fuchsin stain at that time we notice the apical margin of the epithelial cells is red-violet. Daily fluctuations in the quantity and quality of the secretion as well as in the ratio between mucus and glycogen may point to abnormal ovarian function. The aldehyde-fuchsin reaction is easy to perform and suitable for routine studies. Another stain recommended for demonstrating acid mucopolysaccharides and equally as easy to perform is the *alcian blue stain* (method: ROMEIS, 1968, § 2077). When combined with the PAS reaction, the double-staining enables the acid mucopolysaccharides to be distinguished from the neutral mucopolysaccharides and from glycogen (RUNGE *et al.*, 1956).

The demonstration of lipids: In paraffin sections of endometrium the total lipids are stained best with *Sudan Black B* (method after LISON: ROMEIS, 1968, § 1055). The other Sudan stains used to stain frozen sections are of no value for routine diagnostic studies, because the soft, fragmented endometrial tissue is too difficult to section with the usual freezing microtomes. Sudan Black B is especially useful for staining foam cells in the endometrial stroma; these are a sign of hyperestrogenism. Phosphatides are well demonstrated with BAKER's *acid hematein test* (PEARSE, 1968, p. 689) or with the *Luxol-fast blue stain.* Cholesterol and its esters may be detected with SCHULZ's *method* (PEARSE, 1968, p. 702) or with polarized-light since crystals of cholesterol are doubly refractive.

Many additional histochemical and particularly enzyme-histochemical techniques may be employed that may help to detect or clarify subtle variations in the physiological and pathological behavior of glands and stroma. Before we resort to these complicated methods, however, we should ask pertinent questions or have specific research purposes in mind, since the techniques are all too complicated, expensive and time-consuming to be employed as routine methods for daily diagnostic studies. SCHMIDT-MATTHIESEN (1963) applied these special methods to the normal endometrium and compiled his results for ready reference. Later, when we discuss functional disturbances of the endometrium we shall examine in detail the uses and value of these special methods for the histological diagnosis of pathologic states. In performing the methods we have followed PEARSE's recommendations.

The technique of *fluorochromation with acridine-orange* (SCHÜMMELFEDER, 1950; SCHÜMMELFEDER *et al.*, 1957) is too important to go unmentioned. With that technique we not only can follow the daily changes in the menstrual cycle, as with sections stained with hematoxylin-eosin, but we can also detect the first signs of hormonal action: by demonstrating RNA in the nuclei and cytoplasm of endometrial cells we are able to evaluate the effect of estrogen; by demonstrating the first droplets of glycogen in the glandular epithelium we can measure the effect of progesterone (DALLENBACH and DALLENBACH-HELLWEG, 1968). The technique, too difficult for routine studies, has value in research work for revealing subtle changes not evident with other methods. If compared with sections stained with hematoxylin-eosin, it induces us to look for equivalent changes in these.

Besides the histochemical methods, quantiative techniques such as *morphometry* (BISWAS and FINBOW, 1975), *karyometry* (WITT, 1963) or *cytometry* (KAISERLING, 1950; STÄHLER, 1950) may be of diagnostic value. The measurements obtained with these methods must be carefully and critically evaluated since various endometria often shrink differently although embedded under like conditions. In general, with practice in studying cellular details one can do without these measurements in routine dignostic studies.

The culture of endometrium *in vitro* is mainly of scientific interest (for review of literature see HELLWEG and SHAKA, 1959). Nonetheless, by adding hormones in various concentrations and combinations to cultures and comparing these with untreated controls it is possible to gain valuable information about the sensitivity of endometrial tissue as it grows isolated from ovarian influences. When combined with other research methods, endometrial organ culture in particular can be ideally used to study hormonal binding and mode of action (CSERMELY *et al.*, 1969).

Among the many techniques for *chromosome analysis* (HUGHES and CSERMELY, 1965; SHERMAN, 1969), three were found to be reasonably useful in obtaining cells for karyotyping: a) the direct squash preparation of endometrium, b) the tissue-culture squash preparation, and c) the air-dried cell-suspension. One must be cautious about making or accepting diagnoses of aneuploidy with these techniques since the cells are badly disrupted during the squashing procedure.—Skepticism is also warranted for the modern trend to employ *computer programs* for evaluating single parameters, since such studies tend to place the diagnoses from individual patients in question (BEZEMER *et al.*, 1977).—The complicated and technically involved methods for *detecting receptors* for steroid hormones in endometrium have been described by BAULIEU *et al.* (1979), and JENSEN (1979), who should be consulted for details.

5. Components of Curettings and Their Diagnostic Value

The histological diagnosis of curettings is much more difficult than that of endometrium intentionally selected from a definite region of a surgically-removed uterus. We must not only decide from what parts of the uterine cavity and endometrial layers the haphazardly admixed curettings came, we must also be able to diagnose the stage of endometrial development, for from that we date the endometrium (determine as accurately as possible what day of the menstrual cycle the endometrial changes represent), and make our functional diagnosis accordingly. Such goals presuppose a thorough knowledge of the histology of the normal endometrium and its layers in the fundic, isthmic and cervical regions, as well as a knowledge about how reliable these different regions are for establishing accurate diagnoses. Only endometrium from the fundus is suitable for diagnosis; the middle layer of the *functionalis*, that part between the superficial compacta and the basal spongiosa, is particularly ideal. In contrast, the *basalis* generally is of little diagnostic value except in two diseases: in carcinoma or its precursors and in irregular shedding of the endometrium. In most endometria the functionalis is distinct and easy to recognize. We should remember, however, that neighboring glands and stroma may vary somewhat in development without these variations implying that ovarian function is abnormal. In addition, the fragments of endometrium often are from different layers or regions of the endometrium (cornual, fundic, isthmic) that normally show variances in their development. Irregular development is best detected in larger fragments of tissue where the structural units retain their relationships.

Endometrium from the *isthmic portion* of the uterus is unsuited for functional diagnosis since its glands fail to undergo changes during the menstrual cycle

(DANFORTH and CHAPMAN, 1949) or only in exceptional instances (STIEVE, 1928; OBER *et al.,* 1958) and then only slightly. The isthmic mucosa may also give the false impression that the endometrium is atrophic or deficient, or only from the basalis. An experienced investigator will easily recognize and know how to evaluate the uniformly low, relatively avascular mucosa of the isthmic region, with its characteristic flattened, slit-like glands and dense fibrous stroma of small cells. Its glands are cystic only occasionally. Their cytoplasm contains no mucous substances, but histochemically shows, compared with the adjacent endocervical and endometrial glands, a surprisingly high enzymatic activity (PFLEIDERER, 1974). In contrast, the glands of the basalis branch more, and the supporting stroma about them is more irregular since the collagenous fibers anchoring the basalis to the myometrium extend in all directions. In addition, the stromal cells of the basalis remain refractory to hormones, whereas the stromal cells of the isthmic mucosa may at times undergo slight cyclic changes like the stromal cells in the functionalis of the corpus endometrium. When studying entire uteri we should remember that during life the mucosa of the uterine isthmus undergoes physiological displacement, moving with the advance (eversion) and retraction (inversion) of the cervical mucosa (OBER *et al.,* 1958). Accordingly, in the reproductive years fragments of isthmic mucosa should be found among curettings from the cervix (since the isthmus has shifted below the internal uterine os). In the menopause, however, portions of the isthmic mucosa will be among the endometrial curettings since the isthmus has retracted above the internal os.

Recognition of the *endocervical mucosa* presents no problem because its glands and stroma characteristically differ from those of the endometrium. In contrast to the endometrium, the endocervix is furrowed with glands that widely branch and continuously secrete mucus (LANG and SCHNEIDER, 1960). The endocervical mucosa undergoes either no changes during the menstrual cycle (TOPKINS, 1949; DUPERROY, 1951) or at most only slight changes (WOLLNER, 1937; SJÖVALL, 1938). These are mainly quantitative differences in the stages of secretion. All stages however may be found at any time of the cycle. Usually during the early secretory phase most glands disclose basal vacuolation, whereas in the late secretory phase most are dilated, distended with inspissated mucus. Histochemically, the glandular cytoplasm discloses its greatest enzymatic activity during the second week of the cycle (PFLEIDERER, 1974).

Fragments of squamous epithelium from the *portio vaginalis,* often caught up among the curettings, should be carefully inspected and reported in the diagnosis, a principle that well applies to all constituents of the curettings. The height of the squamous epithelium may provide information about the patient's hormonal state or point to a hormonal disturbance, especially when the endometrium is unremarkable, perhaps because its cells are refractory to hormones owing to their inability to make hormonal receptors. In addition, a dysplastic change of the epithelium of the portio may incidentally be discovered in a curetting.

The pathologist should also notify the clinician how much *myometrium* is included with the curettings, for such information helps the gynecologist to draw conclusions about the consistency of the uterine tissues or about his technique of curettage. Further, portions of myometrium may be important in evaluating the extent of a pathological change as, for example, with inflammation of the

endometrium or with invasion by trophoblastic cells. At times the myometrial tissue in curettings originates from a *submucosal leiomyoma,* and in some instances the entire tumor if small may be included in the curettings (Fig. 1). For deciding whether the muscular tissue is from the myometrium or from a leiomyoma, we apply the same criteria as used with larger pieces of tissue. The muscle fibers of leiomyomata are more compact, arranged in tight whorled bundles bound by condensed interstitial collagenous tissue. If mucosa still adheres to the fragment of leiomyoma, then it is usually stretched out and flattened with its glands compressed and narrow, running almost parallel to the surface. In contrast, the mucosa adherent to fragments of myometrium more commonly consists of portions of basalis.

Extensive *regions of necrosis* in curettings may have various causes. Therefore, when endometrial structure in these regions is totally effaced, we are able to reach a diagnosis only if enough preserved endometrial tissue also is present for study. Common examples in which extensive necrosis may be found are: a degenerating carcinoma, an infected (septic) abortion, a degenerated submucosal myoma, and an infarcted polyp. Special stains occasionally may be used in establishing a diagnosis (see above). After a partial abortion the curettings of the retained products of conception may disclose not only variably degenerated or necrotic remnants of *placenta and decidua* but may also reveal several fetal structures at various ages of development or at different stages of maceration. Such fetal parts, surrounded by actively proliferating endometrium, may often be demonstrated weeks to even months after the abortion, serving as proof that an abortion had occurred although it may have been missed clinically. Of all fetal structures the *bony parts* persist the longest and may ultimate-

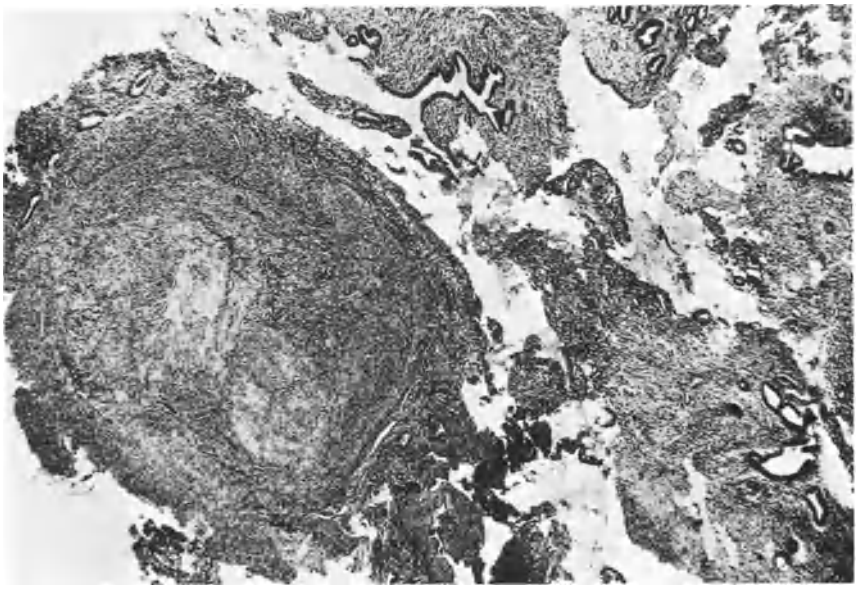


Fig. 1. Submucosal leiomyoma included in curettings, covered in part by a stretched-out and compressed mucosa

ly induce an endometritis. Such cases, however, are rare. The parts of the products of conception most frequently retained after an abortion are the necrotic or hyaline remnants of decidua. These usually appear as vague, shadowy outlines of the original decidual cells. In the differential diagnosis we must distinguish these remnants from the hyaline thrombi of glandular-cystic hyperplasia that are always devoid of a fibrous network, as a reticulum stain will prove. Moreover, the thrombi stain pale violet with the PAS reaction, whereas the decidual remnants stain bright red (ELSTER and SPANKNEBEL, 1959).

Foreign bodies brought into the uterine cavity from the outside belong to the group of rather rare constituents of curettings. The extraneous material may become embedded and "healed into" the endometrium, inducing a foreign-body, granulomatous reaction around it. From the character or age of that reaction we may be able to judge when the foreign material entered the uterus. A foreign-body reaction follows contamination of the uterine cavity with non-soluble particulate matter, for example with talcum crystals. These may be identified under polarized-light as the cause of a granulomatous reaction since they are double refractive. A foreign body reaction may occasionally develop in the endometrium after intrauterine instillation of a liquid tissue adhesive for sterilization.

We must take care not to misinterpret *artefacts*. Not infrequently artifical changes are produced in the soft endometrial tissue by the squeezing and tearing of curettage and subsequent handling; as a result, the endometrial structures become greatly distorted. Occasionally when glands are squeezed or compressed, their lining epithelium intussuscepts to lie within the lumen. Only an experienced pathologist can distinguish such an artefact from an adenocarcinoma (Fig. 2). Even the stroma may become so altered by compression that it may at first glance suggest a sarcoma.

Finally, we must consider *what should not be a component of a curetting*. Occasionally when several curettings are prepared for embedding and placed in perforated tissue-capsules to facilitate the diffusion of dehydrating fluids, a small fragment of tissue from one capsule may slip through a perforation and be carried into another capsule. We should always think of that possibility. If we find a single tiny fragment of tissue that seems from its composition to be foreign and unrelated to the other fragments in the section, we must interpret that unique fragment with caution. One should not try to diagnose an abortion from a single placental villus in curettings that show no other evidence of a previous pregnancy. A much more serious error would be to diagnose a carcinoma from a small fragment of tissue that as a contaminant has unknowingly been caught up in the endometrial curettings of another patient. In such instances, however, to avoid overlooking a carcinoma it is advisable to section the tissue-block at deeper levels so a search can be made for eventual larger fragments of tumor. If the small fragment is found to unite with a larger piece of endometrium, then it matters little how small it is; it is obviously of diagnostic importance. In like manner, if deeper sections prove a single placental villus is attached to a larger fragment of endometrium, the villus on that account may be used to diagnose a previous abortion. Fragments of tissues that do not belong in curettings, for example fat tissue, *indicate* that *contamination* occurred, provided

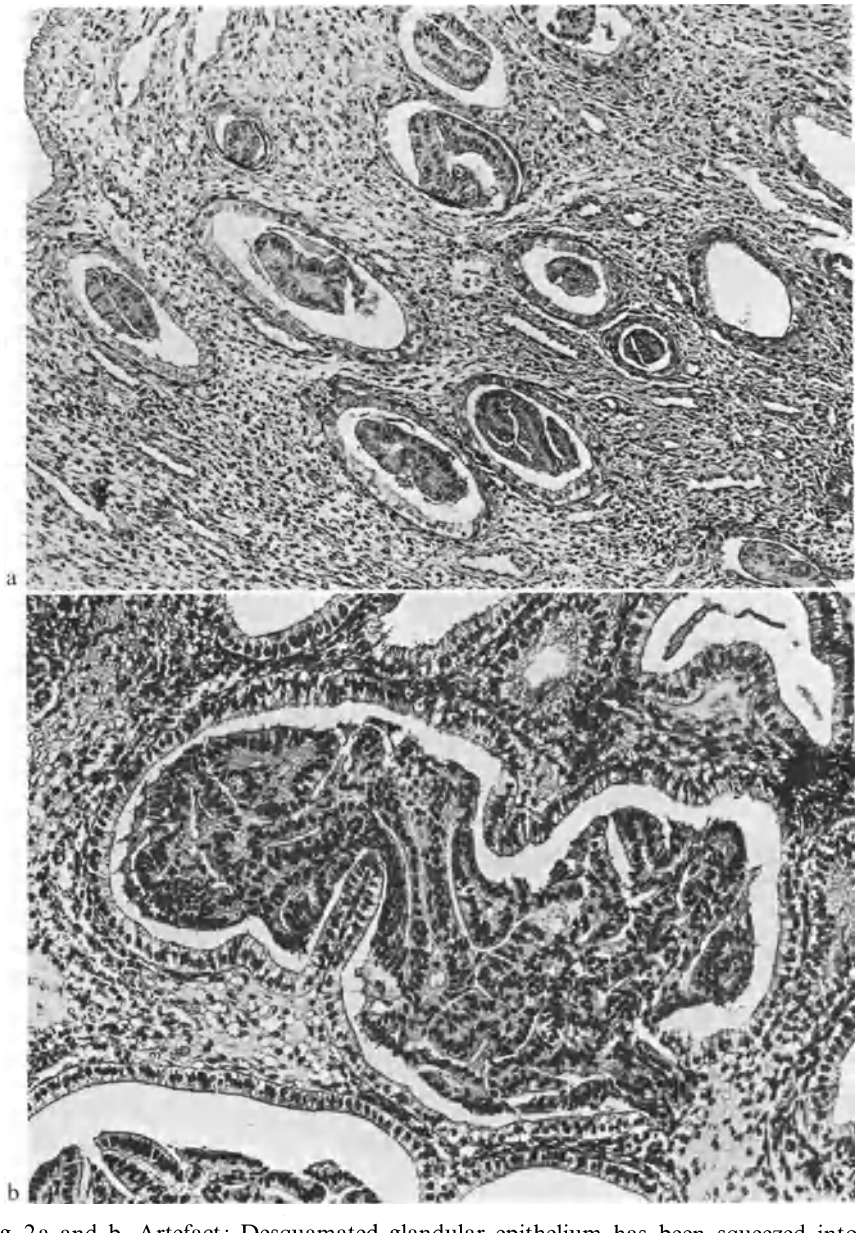


Fig. 2a and b. Artefact: Desquamated glandular epithelium has been squeezed into the glandular lumina. (a) Low magnification. (b) Higher magnification

the uterus was not perforated. If the foreign fragments of tissue are large then it is probable they became mixed with the curettings before the tissues were prepared for embedding.

The **concluding diagnosis** of a histological report of an endometrium should be as comprehensive as possible. That is to say, it should include the pathological

Table 2. Factors limiting the diagnosis of endometrial curettings

Referring physician:	absent or inaccurate clinical data curettage at the wrong time insufficient curettings incorrect handling or fixation of the material
Pathologist:	inadequate experience incomplete preparation of the material poorly prepared microscopic sections
Endometrial tissue:	changes in morphology lag behind the changes in function (differences in tempo) transition between benign and malignant not clearly detectable (differences in stages) functional changes with no corresponding morphological (histological, histochemical) changes detectable

diagnosis of the structural changes, and the diagnosis of the corresponding functional state. Provided he has submitted sufficient tissue for study, the gynecologist has a right to expect an explicit pathological report on which he can base his treatment of the patient. The clinician is not benefited by a long account of vague assumptions or a list of the different diagnoses that might be possible. The pathologist should endeavor to reach a precise final diagnosis. With rare exceptions (see Table 2) he will succeed in doing so if he carefully studies the material and uses the appropriate diagnostic aids (special stains and techniques) that are available.

6. Statistical Analysis of the Histological Results

The primary purpose of the histological study of surgically-removed tissue is to provide as accurate a diagnosis of the morphological changes present as possible. In addition, however, the study should stimulate scientific interest and encourage questions, and should be employed to investigate these questions. Only with such precepts can a dynamic, intellectually stimulating diagnostic service be guaranteed that will always remain receptive to new scientific information.

With that purpose in mind, our pathology service uses a dual system of cataloguing specimens received for study. The first system consists of an alphabetical registry of the names of all our patients: an index card is used for each patient; it bears the specimen number and code number of the final diagnoses of every specimen of tissue received from that patient. The system allows a rapid "histological anamnesis" of every patient, for from the record of previous studies one may quickly evaluate the advance or regression of changes, may search for or review possible interrelationships between diseases, or may learn about their final outcome. The second system represents a registry of the diagnoses, using a scheme with decimal numbers that we designed for our clinic. Each diagnosis of normal or functionally disturbed endometrium is given a

Table 3. Statistical analysis of functional changes of the endometrium (altered ovarian function) using the decimal system

	Regeneration	Proliferation	Secretion	Menstrual shedding	No functional changes
Regular cycle	10	20	30	40	50 resting
Shortened cycle	11	21	31	41	51 atrophic
Delayed cycle	12	22	32	42	52 cystic atrophic
Insufficient cycle	13	23	33	43	
Irregular cycle	14	24	34	44	54
Glandular-cystic hyperplasia	15 adaptation hyperplasia, post partum and post abortum	25 glandular cystic hyperplasia resting and active form	35 hyperplasia with secretory change	45 remnants of hyperplasia after extensive shedding	55 regression of hyperplasia
Adenomatous hyperplasia and stromal hyperplasia	16	26	36	46	
Focal hyperplasia and hyperplasia of basalis	17	27	37 Secretory hypertrophy	47	57
Breakthrough bleeding	18	28 anovulatory cycle	38 (also ovulatory bleeding)	48 hormonal withdrawal bleeding	58 apoplexia uteri

number of two digits (see Table 3). When contraceptive hormones had been taken by the patient, "ov" is added to the number, when other hormones had been administered, "hz" is added. The diagnoses of organic (primary) diseases of the endometrium, such as endometritis, carcinoma etc., receive numbers of three digits, as do the diagnoses of other gynecological organs (see tables in STOLL and DALLENBACH-HELLWEG, 1968; compare with STOLL and RIEHM, 1954). As soon as we finish our histological report, we select from our coded list of pathological conditions the appropriate number for the diagnosis. When the secretary writes the report she enters the code number on the patient's card in the alphabetical registry. Such a cataloguing system enables us, on the one hand, to collect and utilize the material we have diagnosed for later scientific study. It obviates tedious searching through volumes of bound reports by an assistant or doctoral student, who may be working on a research project. On the other hand, it helps in teaching by making it possible for us to plan and prepare demonstrations and clinical-pathological conferences on short notice.

B. The Normal Histology of the Endometrium

1. The Individual Structures

The endometrium of the corpus is composed of two layers: the basalis (the layer from which the endometrium regenerates after menstrual shedding) and the overlying functionalis. In the second half of the menstrual cycle, the functionalis may be differentiated into the superficial compacta and the underlying spongiosa, which extends to the basalis. During the menstrual cycle the endometrium varies from 1 mm (postmenstrual) to about 8 mm at the end of the third week. Every layer consists of two major components: the epithelial component, either as glands or as superficial epithelium, and the mesenchymal component of stromal cells with pluripotential properties.

As a target-organ under control of the ovarian hormones, the endometrium is rhythmically called upon to rapidly fulfill functional requirements that necessitate frequent remodeling of its structural components, implying rapid and well-adapted changes. To find out how these changes take place and how they are controlled by the ovarian hormones, we shall examine the basic structures of these components involved without, however, going into great detail. For the reader who desires a more thorough discussion of the normal, sexually-mature corpus endometrium, I highly recommend SCHMIDT-MATTHIESEN's book (1963). This excellent monograph provides details of normal endometrial histology, karyometry, electronmicroscopy, and histochemistry. Significant new discoveries of recent years are described in the following pages.

a) The Glandular Epithelium

is a single layer of columnar epithelial cells. Their height varies, depending on the functional (hormonal) state, from 6 μ postmenstrual to 20 μ at the end of the proliferative phase.

During the proliferative phase the *nuclei* of the glandular cells are elongated and have a dense chromatin. Between the tenth to the sixteenth day of the cycle their content of DNA reaches its maximum (VOKAER, 1951; HARKIN, 1956; MOOKERJEA, 1961; FETTIG and OEHLERT, 1964; FETTIG, 1965; NORDQVIST, 1970). During the secretory phase the nuclei become round, vesicular, and gradually lose DNA. The chromosome sets are mostly diploid (79 per cent according to STANLEY, 1969), showing a consistant pattern of 46 XX (SHERMAN, 1969). Aneuploidy apparently never occurs (WAGNER *et al.*, 1968). Mitoses are most numerous just before ovulation. JOHANNISSON and HAGENFELDT (1971) found an accumulation of nuclei in the S-phase between cycle days 14 and 22 and suggested therefore that the synthesis of DNA in the human endometrium was synchronized.

The *nucleoli* contain abundant RNA. In contrast, the RNA of the cytoplasm reaches its greatest concentration after ovulation. The nucleoli of the early proliferative phase are finely granular and compact. They enlarge as mid-cycle is approached and may reach 2.8 μ in diameter (FASSKE *et al.*, 1965). During the first week of the secretory phase the nucleoli contain a characteristic tubular or meshwork-like structure, the nucleolar channel-system, which is embedded in an electron-dense matrix and contains RNA; some investigators believe it serves the exchange of protein between nucleolus and cytoplasm primarily for enzyme synthesis (DUBRAUSZKY and POHLMANN, 1960; CLYMAN, 1963; ANCLA and DE BRUX, 1965; TERZAKIS, 1965; MORE *et al.*, 1974), for example, for the rapid transport of specific, progesterone-induced ribonucleoprotein (ARMSTRONG *et al.*, 1973). The channel-system apparently occurs only in human endometrium and seems to depend on adequate levels of progesterone. It may be induced *in vitro* (KOHORN *et al.*, 1970) or experimentally (NAKAO *et al.*, 1971) when enough gestagen is administered. At the end of the menstrual cycle it is discharged into the cytoplasm and taken up by lysosomes. FELDHAUS *et al.* (1977) were able to demonstrate the system shortly before ovulation.

During the proliferative phase the *cytoplasm* is unusually rich in RNA, as disclosed by histochemical techniques (WISLOCKI and DEMPSEY, 1945; ATKINSON *et al.*, 1949; BREMER *et al.*, 1951; MCKAY *et al.*, 1956; MOOKERJEA, 1961; BOUTSELIS *et al.*, 1963; GROSS, 1964), by fluorescence microscopy (BONTKE, 1960; DALLENBACH and DALLENBACH-HELLWEG, 1968) and by autoradiography (FETTIG, 1965). Electron-microscopic studies (BORELL *et al.*, 1959; CARTIER and MORICARD, 1959; WESSEL, 1960; WETZSTEIN and WAGNER, 1960; DUBRAUSZKY and POHLMANN, 1961; GOMPEL, 1962, 1964; THEMANN and SCHÜNKE, 1963; MORICARD and MORICARD, 1964; MORICARD, 1966; WYNN and HARRIS, 1967; WYNN and WOOLLEY, 1967) indicate the cytoplasm, especially that of the basal parts of the cells, contains abundant ribosomes, some bound to endoplasmic membranes, some free. Towards the end of the proliferative phase the Golgi complex located above the nucleus becomes visible with secretory granules (probably acid phosphatases; NILSSON, 1962). At the base of the cell near the first aggregates of glycogen the mitochondria multiply and enlarge. With the onset of the secretory phase the previously rough endoplasmic reticulum becomes smooth. Abundant basal secretory granules then collect around these smooth endoplasmic membranes, and they in turn gather about the enlarged mitochondria. As glycogen, mucopolysaccharides and proteins accumulate at the lower pole of the nucleus to form cloudy or granular deposits, the large mitochondria nearby swell to giant sizes, and may reach 7 μ in diameter. They have compact cristae and up to eight intramitochondrial filaments of DNA (MERKER *et al.*, 1968; ARMSTRONG *et al.*, 1973). On the seventeenth day of the menstrual cycle glycogen is found scattered throughout the cytoplasm, and the well-developed Golgi complex with terminal vacuoles is located above the nucleus. With the onset of secretion on the nineteenth and twentieth days the cytoplasm along the luminal surface sends out enlarged microvilli filled with secretory products. Shorty thereafter the apical portion of the cell is discharged into the lumen. Thus, the epithelial cells expel their products by apocrine secretion, thereby becoming smaller. Because minute

amounts of glycogen are apparent in the glandular cells with the electron-microcope several days before ovulation through to the last week of the cycle (with a distinct maximum between the sixteenth and twentieth days), the glycogen is thought to serve a complex function involving more than pure glandular secretion (SAKUMA, 1970; JOHANNISSON and HAGENFELDT, 1971). Besides glycogen, the glandular cells also excrete neutral and acid mucopolysaccarides (SALM, 1962; STRAUSS, 1963), and lipids. Most accumulate at the apical cell-border and are either carboxymucins or sulphomucins (SORVARI, 1969). Fine droplets of non-double refractive lipids may be detected during the secretory phase, chiefly in the basal cytoplasm of the glandular epithelium. Since the appearance and quantity of the droplets are influenced by hormones, some investigators believe the lipids indicate increased cellular activity induced by progesterone (ASCHHEIM, 1915; BLACK *et al.*, 1941). Other authors (FROBOESE, 1924; CRAIG and DANZIGER, 1965), however, regard the lipid droplets as products of degeneration. Their occurrence in the glandular epithelium of the decidua of a young pregnancy, however, favors the first view. By the twenty-second day of the cycle only a few secretory granules remain. By the twenty-third and twenty-fourth day the granular endoplasmic reticulum has involuted.

The apical *surface* of the epithelial cells in the proliferative phase possesses elongated delicate microvilli which contain alkaline phosphatases (BORELL *et al.*, 1959). During the secretory phase, as these microvilli draw back and disappear, the activity of alkaline phosphatase diminishes.

The *substance secreted* by the glandular epithelial cells and found within the glandular lumina is chemically complex, and its composition varies with the phase of the menstrual cycle. During the proliferative phase it consists of a mixture of desquamated superficial glandular cells, RNA, proteins, and acid mucopolysaccharides. During the secretory phase the secretion appears as globules, which contain rounded aggregates of glycogen, acid and neutral mucopolysaccharides, proteins, peptides, neutral lipids, phosphatides and numerous enzymes. During the fourth week of the cycle the globules degenerate; at first they appear amorphous but later they become homogeneous. With that change they take on a β-metachromasia that is resistant to alcohol and ribonuclease. Finally, the glycogen disappears, leaving polysaccharides that are resistant to diastase. The metachromasia thereby increases.

Occasionally it is possible to find a *ciliated cell* among the glandular epithelial cells (MANDL, 1911). The ciliated cells initially lie against the basement membrane, and because of their abundant translucent cytoplasm can readily be recognized as "clear cells". Their rounded nucleus is generally located above those of the neighboring epithelial cells (FEYRTER and FROEWIS, 1949). In 1950 HAMPERL described a ciliary vesicle in these cells which, he explained, moved upwards through the cell to protrude at the upper surface, releasing its cilium to the outside. Later the ciliary border is shed by apocrine mechanisms. With the electron microscope it is possible to follow the development of the cilia from the basal corpuscles within the cytoplasm. The corpuscles form as the centrioles replicate and migrate to the cell surface where the vesicle develops. Each cell always has just eleven cilia. Their ultrastructure varies more than that of cilia in other organs (HANDO *et al.*, 1968). They can be easily demonstrated with FEYRTER's

"thionine-enclosure-stain" because their content of mucoprotein makes them appear dark.

The number of ciliated cells fluctuates considerably from patient to patient, probably depending on the functional state of the endometrium (that is, on ovarian function). DAZO *et al.* (1970) report ciliated cells are more abundant close to the tubal cornua and the endocervical mucosa. "Clear cells" as possible precursor cells are commonest in the proliferative phase and in glandular-cystic hyperplasia. Fully-developed ciliated cells are most numerous around mid-cycle and in hyperplastic endometria (MADDI and PAPANICOLAOU, 1961; SCHUELLER, 1968; 1973). In atrophic endometrium they are virtually non-existent (PAPADIA, 1959; FLEMING *et al.*, 1968). From these facts we could assume that estrogen stimulates the cilia to develop (SCHÜLLER, 1961, 1968, 1973). No clear concepts exist regarding their function. Some investigators have postulated that the cilia aid in removing the secretions discharged by the neighboring cells. In their electron-microscopic studies of endometrium of the secretory phase, MORE and MASTERTON (1975) described a transformation of ciliated cells into secretory cells, a change that would explain the apparent decrease in ciliated cells during the second half of the cycle.

In addition to the ciliated "clear cells", apparently other *clear cells* become visible in the glandular epithelium. Cells in the early prophase of mitosis (FUCHS, 1959) or degenerating cells with karyorrhexis (ROTTER and EIGNER, 1949) may also appear as clear cells. Further, lymphocytes and polymorphonuclear leukocytes that migrate through the glandular epithelium may swell up, their cytoplasm becoming conspicuous and clear. FUCHS points out that the nuclear changes found in some of the clear cells, with the disappearance of the nucleoli and the increase in chromatin, are characteristic of the onset of mitosis. The great increase of clear cells in glandular-cystic hyperplasia found by all investigators parallels the rise in mitotic rate of the hyperplastic epithelium. In contrast, SARBACH (1955) believes some of the clear cells represent degenerating forms developing after an unsuccessful mitosis caused by excessive stimulation with estrogen. MÜLLER (1951) and FEYRTER (1952) assumed the clear cells were active as endocrine cells. FEYRTER even included them among the clear cells of the "generalized endocrine organ of epithelia" which he described. Several facts, however, oppose his assumption. The cells contain only meager amounts of RNA, suggesting they are inactive. Their Golgi apparatus is poorly developed (WESSEL, 1960) and they possess few enzymes, secretory granules or lipids. They are neither chromaffin, argentaffin, nor argyrophilic.

b) The Superficial Epithelium

during the proliferative phase closely resembles the glandular epithelium, although it contains greater numbers of ciliated cells than does the glandular epithelium (FERENCZY *et al.*, 1972). At the onset of the secretory phase however it lacks the apical accumulation of acid mucopolysaccharides (LEWIN, 1961; SCHMIDT-MATTHIESEN, 1963). Neutral mucopolysaccharides as well are very sparse. Yet, glycogen appears in the superficial epithelium earlier, in larger amounts, and

remains longer than it does in the glandular epithelium. Its activity of acid phosphatase is lower then in the glandular epithelium but its content of phosphatides is higher (SCHMIDT-MATTHIESEN, 1968). Noteworthy is the uniformly high content of RNA in its cytoplasm and nucleoli during the whole cycle (BREMER *et al.*, 1951), suggesting that a synthesis of protein persists. Thus, the superficial epithelium also differs from the glandular epithelium functionally. That difference is easy to understand when we consider how important its secretion might be for the adherence and implantation of the blastocyst. As revealed by scanning electron microscopy, the ciliated cells accumulate about the mouths of the glands (HAFEZ *et al.*, 1975). During the secretory phase the cilia degenerate, and as the apical surface of the cell continues to bulge into the uterine cavity, the size and number of its microvilli decrease (JOHANNISSON and NILSSON, 1972).

c) The Stromal Cells

The endometrial stroma consists of pluripotential mesenchymal cells, which at the beginning of the menstrual cycle are uniformly spindle-shaped, poorly differentiated, and joined to one another by cytoplasmic processes. The cells lie firmly anchored within a delicate network of reticulum fibers. Their elongated nuclei have abundant chromatin and they show in radioautographic studies a well-defined synthesis of DNA (FETTIG and OEHLERT, 1964), reflecting the DNA-controlled synthesis of RNA (MORE *et al.*, 1974). At the beginning of the menstrual cycle the cytoplasm of the cells forms a narrow rim about the dark nuclei. Near the end of the proliferative phase the nuclear substance becomes less dense, the nucleoli grow larger and more conspicuous, and the nuclear membrane becomes wrinkled. In the cytoplasm of the more superficial stromal cells the RNA accumulates, and their smooth and rough endoplasmic reticulum expand. The Golgi apparatus and mitochondria remain poorly developed. Microfibrils of collagen become apparent, not only within the cells but particularly just outside of them (WETZSTEIN and WAGNER, 1960; DUBRAUSZKY and POHLMANN, 1961; WYNN and WOOLLEY, 1967; WIENKE *et al.*, 1968; MORE *et al.*, 1974). During the secretory phase the mitochondria and smooth endoplasmic reticulum increase in number and size, and the Golgi apparatus enlarges, whereas the ribosomes decrease (LIEBIG and STEGNER, 1977). Vacuoles and granules begin to appear in the expanding but shortened cytoplasmic microvilli. From the twentieth day of the cycle on, glycogen and glycoproteins in diffuse and granular form can be demonstrated in the cytoplasm of the stromal cells with electronmicroscopic and histochemical methods (MCKAY *et al.*, 1956). Some stromal cells contain lipids as fine droplets (ASCHHEIM, 1915; FROBOESE, 1924; BLACK *et al.*, 1941; CRAIG and DANZIGER, 1965) which, in contrast to the lipids of the glandular epithelium, are double-refractive and appear after stimulation with estrogen. When the lipids accumulate in large amounts, the stromal cells may reach the size of decidual cells and acquire a foamy cytoplasm. Consequently, they have been mistaken for macrophages or lipophages. It seems more likely they develop because of an overproduction of estrogen, and the lipids may represent a storage form of that hormone or a metabolite of it (DALLENBACH-HELLWEG, 1964). If we consider the experimental studies of FROEWIS and

ULM (1957) and GELLER and LOHMEYER (1959) on the endocrine function of the endometrium, it is understandable why they suggested that the stromal cell might be able to produce estrogen. Certainly its fine structure does not exclude such a possibility. Studies by DALLENBACH and RUDOLPH (1974), however, failed to show that endometrial tissues can produce and secrete estrogenic substances (cf. p. 115ff).

During the second half of the secretory phase the stromal cells of the compacta cease their mitotic activity and differentiate in two directions (Figs. 3 and 4, Color Plate II b): About one half of the cells enlarge to plump, circular *predecidual cells* with vesicular nuclei and abundant clear cytoplasm. Other cells contract to small rounded *endometrial granulocytes,* which are distinguished by their characteristic and bizarre nuclear shapes and by the phloxinophilic granules in their cytoplasm (HAMPERL, 1954; HELLWEG, 1954). Their dark, chromatin-rich nuclei apparently account for the rise in stromal DNA at this time (NORDQVIST, 1970; see color plate II a). As indicated by histochemical studies (HELLWEG, 1956) and ultraviolet microspectrophotometric measurements (HELLWEG and SANDRITTER, 1956) these granules contain a large polypeptide molecule rich in tyrosine and tryptophan. The UV-absorption curve of the polypeptide molecule is virtually identical with that of relaxin. Immunhistological techniques indicated relaxin was probably present in the granules of endometrial granulocytes (DALLENBACH and DALLENBACH-HELLWEG, 1964). Electron-microscopically the cytoplasm of these cells has a well-developed, smooth endoplasmic reticulum. The granules develop within preformed sacculi, which most probably represent dilated cisternae of the endoplasmic reticulum or Golgi complex (CARDELL *et al.,* 1969; JAEGER and DALLENBACH-HELLWEG, 1969; SENGEL and STOEBNER, 1972) (Fig. 5). The activity of esterase and acid phosphatase found in human granulocytes

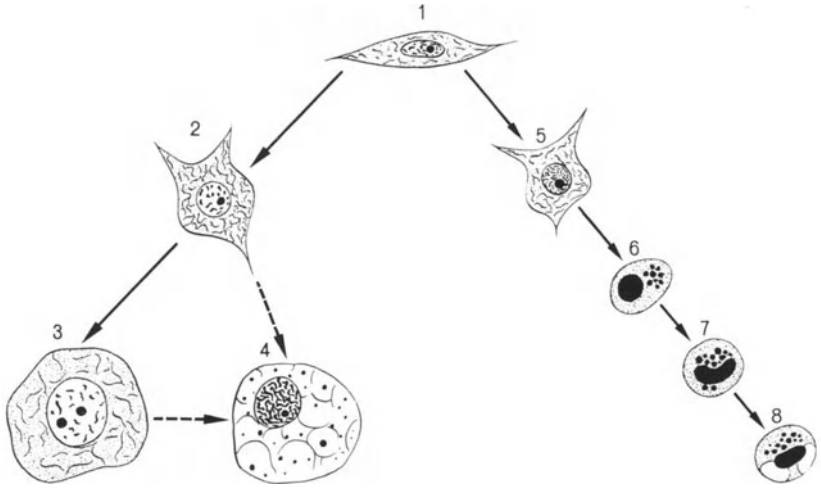


Fig. 3. Schematic portrayal of how endometrial stromal cells differentiate. *1* Poorly differentiated stromal cell, *2* Stromal cell becoming larger and more globular, *3* Decidual cell, *4* Foamy decidual cell ladened with metachromatic granules, *5* Stromal cell becoming smaller and more rounded, *6, 7, 8* Various stages in the development of endometrial granulocytes

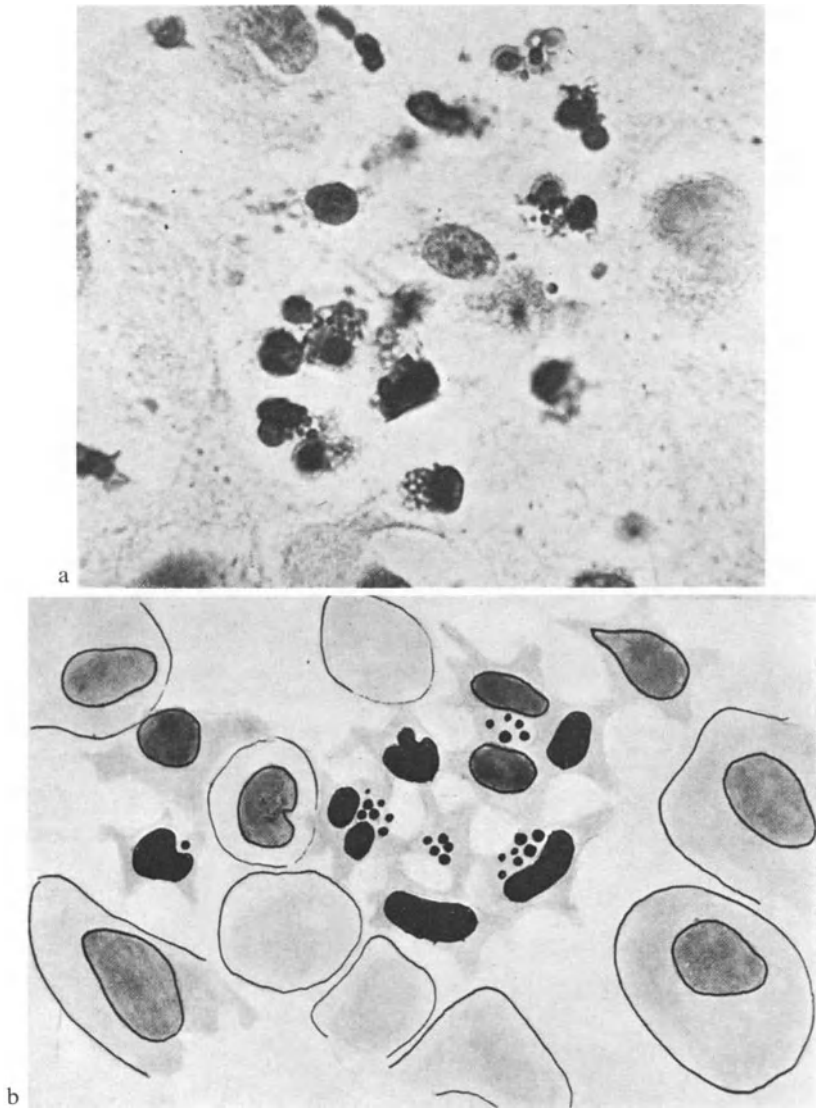


Fig. 4a and b. Decidua, second month. A group of endometrial granulocytes between large decidual cells. (a) Phloxine-tartrazine stain. (b) Schematic facsimile

(JIRASEK and DYKOVA, 1964; personal results) is analogous to the esterase activity demonstrated in the granulocytic cells of the myometrial gland of the rat (BULMER, 1965), also related to relaxin, and to the activity of acid phosphatase detected in the endometrial granulocytes of the monkey (MANNING *et al.*, 1967). These results suggest the granules containing relaxin are possibly bound to lysosomes. That union would guarantee that relaxin stored in the cells would be released at a definite time. Such is the case. The liberation of relaxin takes

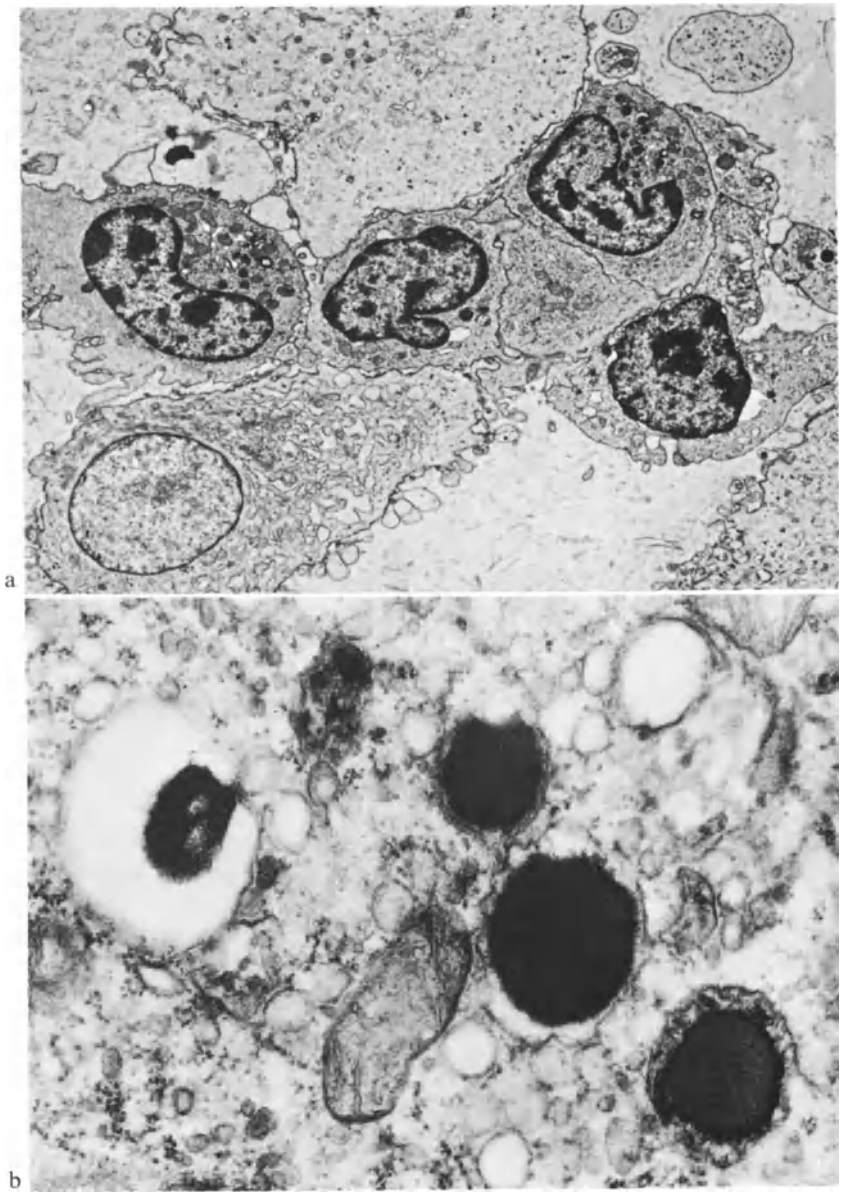


Fig. 5a and b. Decidua, second month. (a) Four endometrial granulocytes between large decidual cells. Lobated nucleus of coarse chromatin network; granules of various sizes in the nuclear recess. Magnification: ×4000. (b) Segment of the cytoplasm of a granulocyte with granules of various sizes within cisternae. Magnification: ×46000

place premenstrually and is dependent on the fall of progesterone, for with the decrease in progesterone the lysosomal membranes become permeable (BITENSKI and COHEN, 1965) (cf. p. 40). As shown by histochemical and electron-microscopic studies, the relaxin liberated in the upper layers of the endometrium

leads to dissolution of the fibrous network, faciliating thereby the dissociation and disintegration of these parts.

If pregnancy results, then the small, motile granulocytes accumulate in large numbers around the site where the blastocyst begins to embed. As nidation proceeds, proteolytic enzymes become activated (STRAUSS, 1964; SCHMIDT-MATTHIESEN, 1967). Relaxin is then released locally for a brief period, inducing a local breakdown of the fibrous network, making it easier for the blastocyst to implant. Thus, the endometrium appears to participate actively in the process of implantation, facilitating and setting limits to the invasion by the trophoblasts (DALLENBACH and DALLENBACH-HELLWEG, 1964; SCHMIDT-MATTHIESEN, 1968). The numerous granulocytes in the remaining stroma, which develops into a decidua, retain their relaxin during the first months of pregnancy (HELLWEG, 1957).

Initially, the young decidual cells exhibit no signs of regression as do the predecidual cells, but contain many slender mitochondria and a prominent endoplasmic reticulum (WYNN and WOOLLEY, 1967). Histochemically they reveal high activities of enzymes (VACEK, 1965); particularly the carbonic anhydrase is increased. Many decidual cells become binucleated, thereby increasing their nuclear surface and indicating they have become more active.

The endometrial granulocytes, about as numerous premenstrually as the predecidual cells, were mistaken originally for polymorphonuclear leukocytes until studies disclosed their true nature. During the normal menstrual cycle the polymorphonuclear leukocytes infiltrate the dissociated endometrium only after menstruation has set in. No leukocyte infiltration of normal endometrium takes place before menstruation begins.

A special type of predecidual cell that occasionally may be seen is the *metachromatic cell* (ASPLUND and HOLMGREN, 1947; MCKAY, 1950; RUMBOLZ and GREENE, 1957; HELLWEG, 1959; Fig. 3). It is distinguished by its foamy cytoplasm with loosely scattered metachromatic granules. Its nucleus is denser then that of the decidual cells and is often seen in mitosis. The significance of the metachromatic cell remains unclear. That it occurs rarely and in sparse numbers suggests some decidual cells are particularly capable of adapting to special demands or stimuli. It may merely represent an aberrant differentiation.

In summary, the endometrial stromal cell differentiates into two main forms, the endometrial granulocyte and the predecidual cell. In the secretory phase both dominate the histological picture in about equal numbers. In comparison, all other cells of the stroma under normal conditions are rare. Among them are the poorly differentiated, pluripotential stromal cells that originated from the Müllerian duct or those derived from the primitive mesenchyme (the vascular and perivascular cells, mast cells, cells of perineurium).

Lymphocytes frequently appear in the normal, non-inflamed endometrium. Since they lack the characteristic phloxinophilic granules they may be easily distinguished from the endometrial granulocytes with special stains. FEYRTER (1957) included the lymphocytes among the "resting wander-cells" and named them the "histiogenic lymphocytic round cells". Although they morphologically resemble the lymphocytes in the circulating blood, it seems likely that the majority arise locally from lymphoid tissue in the endometrium. *Lymphoid follicles* in the endometrium are not unusual (MÖNCH, 1918; SEITZ, 1923; NEUMANN, 1930; MASSEL, 1947; PAYAN *et al.*, 1964; SEN and FOX, 1967). Most probably they

represent merely an exaggerated but physiological reaction of a locally well-developed lymphatic tissue. RAHN and UEBEL (1965) and RAHN (1968) found lymphoid follicles with germinal centers in 50 per cent of normal endometria from women in the reproductive years; (SEITZ reported in 20 per cent). They regarded the follicles as a mechanism of defense against noxious agents, not only exogenous but endogenous as well. The lymphoid follicles appear in all layers of the endometrium and during every phase of the menstrual cycle (Fig. 6). Prepubertal and postmenopausal endometria, however, lack lymphoid follicles (IRWIN, 1956).

The socalled "monocytic round cells" or *histiocytes* (FEYRTER and KLIMA, 1958) perhaps originate from perivascular connective tissues of the endometrium or from wandering monocytes from the blood. They may give rise to various types of phagocytic cells that may occasionally be found in the endometrium, depending on the local requirements or conditions that develop. Thus, we may find lipophages, siderophages, mucophages, cytophages, and others.

Mast cells may also be found in the endometrium. FEYRTER (1957) believed they arose from the stroma. It seems more likely, however, that they infiltrate the endometrium from the circulating blood. Mast cells have been reported by some authors to be more common during the proliferative phase (VON NUMERS, 1942; MCKAY, 1950; RUNGE *et al.*, 1956); by others, more common in the secretory phase (SYLVEN, 1945; RUMBOLZ and GREENE, 1957; GUPTA and SCHUELLER, 1967). According to VARA (1962) their number runs parallel with the height of the endometrium during the endometrial cycle. Presumably the granules the mast cells form during the secretory phase are discharged just before menstruation. Perhaps the differences of opinion about mast cells have arisen because some authors confuse these cells with the metachromatic predecidual cells. ASPLUND and HOLMGREN pointed to that possibility in 1947 and endeavored to establish criteria for differentiating the two types of cells. Most investigators believe the function of the mast cells in the human endometrium is to release heparin and mucopolysaccharides; precise and definite information about their function is lacking, however.

Plasma cells and eosinophils appear in the normal endometrium only rarely (VON NUMERS, 1942; FEYRTER, 1957). Increased numbers of these cells, as well as of polymorphonuclear leukocytes, indicate an inflammatory reaction; all three types infiltrate the endometrium from the blood stream. It is indeed possible, however, that in chronic inflammation lymphocytes locally transform into macrophages or plasma cells, depending upon the kind of inflammatory or antigenic stimulus.

d) The Reticulum Fibers,

in contrast to collagen fibers, may be reformed within a few days, giving rise again to a dense reticular network. While the stroma of the basalis and the isthmic mucosa remains uniformly dense, the content of fibers in the functionalis fluctuates considerably during the menstrual cycle (HÖRMANN, 1908; SEKIBA, 1924; WERMBTER, 1924; CENTARO and SERRA, 1949; STAEMMLER, 1953; DUBRAUSZKY and SCHMITT, 1958; HOFFMEISTER and SCHULZ, 1961). HÖRMANN

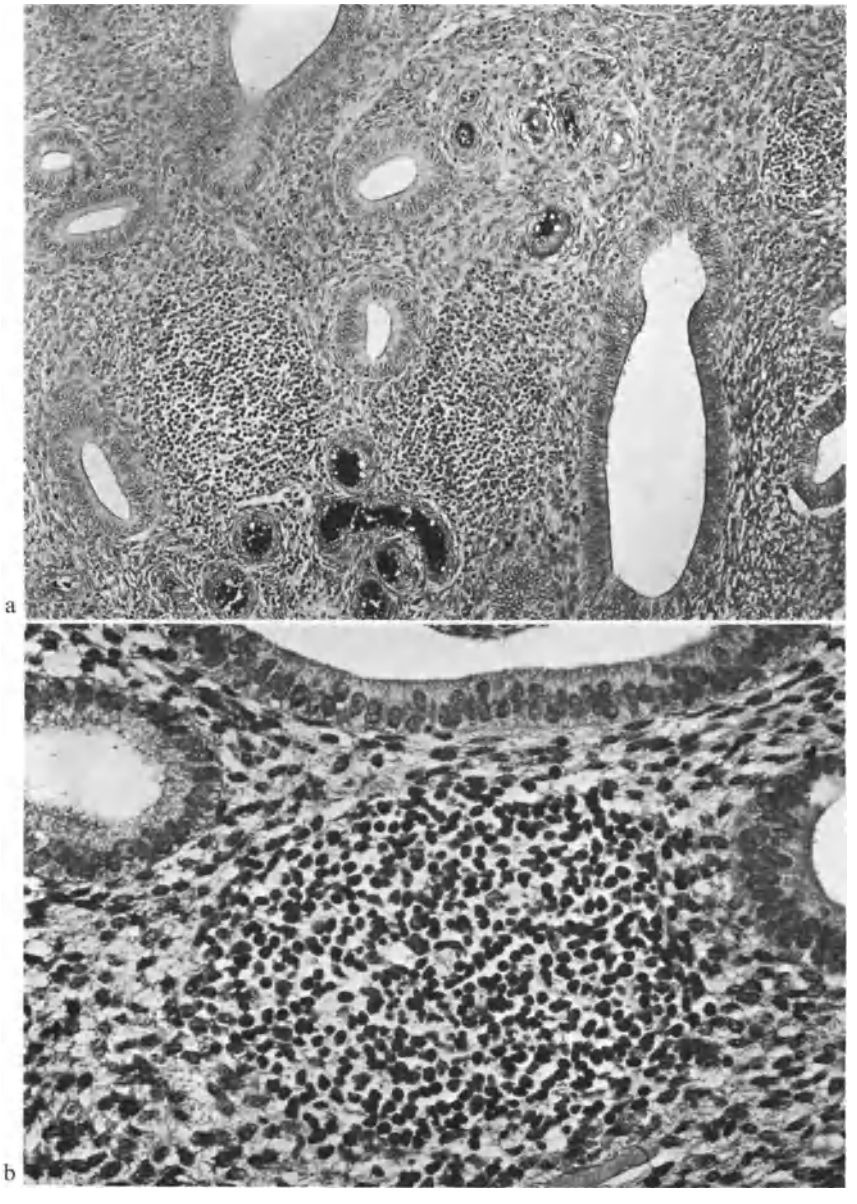


Fig. 6a and b. Lymphoid follicle in endometrial stroma, late proliferative phase. (a) Low magnification. (b) Higher magnification

distinguished between elongated cytoplasmic processes of the cell and an extracellular network of fibers in which the stromal cells are suspended. In electron-microscopic studies HOFFMEISTER and SCHULZ were able to show that the connective tissue fibrils formed within the cells from the first to the fourth day of the proliferative phase; thereafter the fibrils matured extracellularly. With the

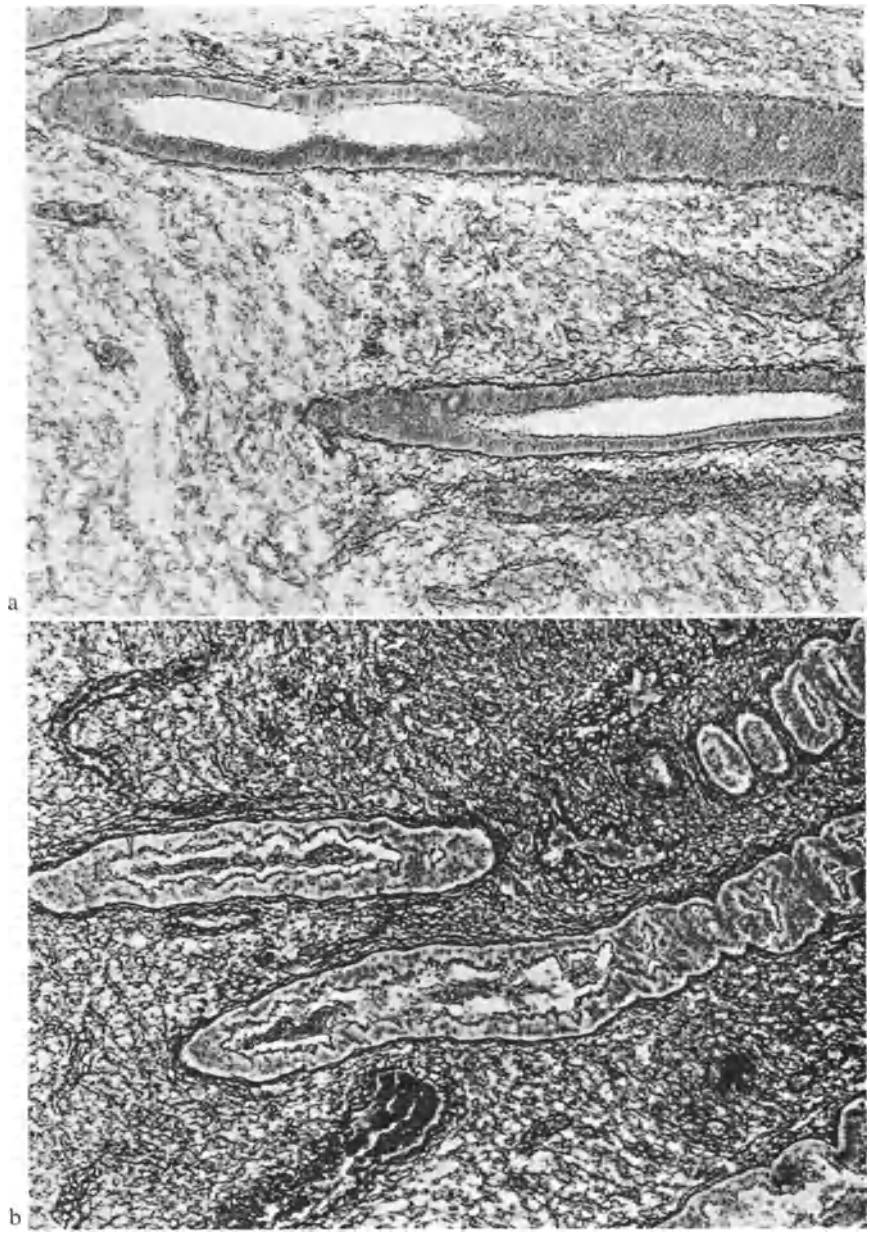


Fig. 7a and b. Reticular fibers of the endometrial stroma. (a) Mid-proliferative phase, (b) Midsecretory phase. Silver impregnation after GOMORI

light microscope, however, only occasional delicate reticulum fibers can be made out during the first eight days of the proliferative phase (Fig. 7a). As ovulation approaches, these fibers become denser and thicker. During the secretory phase they are temporarily pulled apart by the transitory edema that develops. By

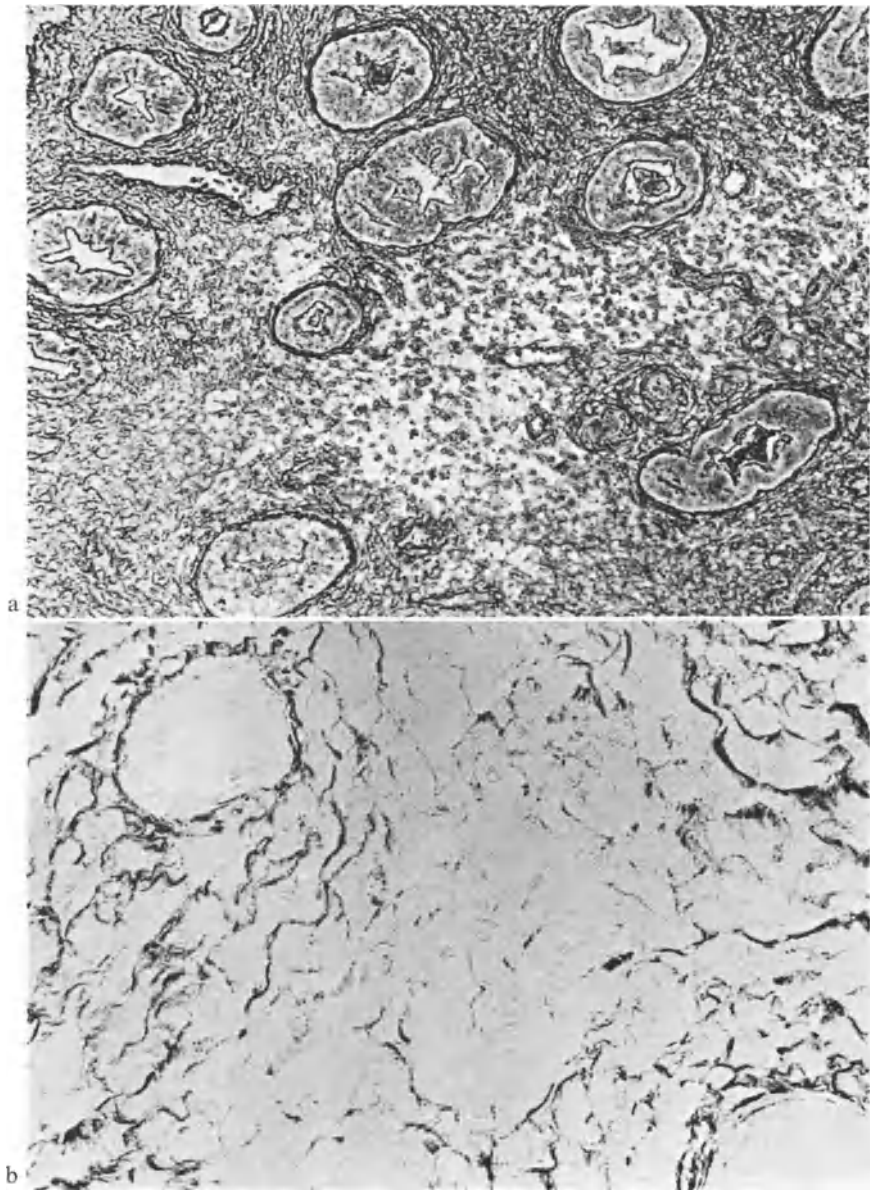


Fig. 8a and b. Predecidual transformation of the endometrium. Focal dissolution of the reticular fibers: (a) In the human endometrium after release of relaxin from the local granulocytes. (b) In the Rhesus monkey after injection of relaxin. Silver impregnation after GOMORI

the fourth week of the cycle, however, they enmesh each predecidual cell and form a dense network about the glands and the spiral arterioles (Fig. 7b). When progesterone decreases and the liberation of relaxin follows, the reticulum fibers disintegrate, at first locally where the granulocytes are located (Fig. 8a), then

shortly thereafter throughout the entire compacta. As a result, the glands separate from the stroma and the stromal cells dissociate from one another. As long as the corpus luteum continues to produce progesterone, however, the reticulum fibers remain intact; in young decidua they form a dense fibrous network. The fibers undergo dissolution only about the site of implantation of the blastocyst where granulocytes accumulate. Since the zone containing the great numbers of granulocytes is limited, a relative deficiency of progesterone, which acts as the stimulus for the release of relaxin, must develop locally on the day of implantation. Hence, we see that the structure of the reticulum network is subjected to functional variations just like other components of the endometrium. From the appearance and quality of the reticulum network we are able to evaluate the functional state of the endometrium, and to determine whether a physiological balance in hormones exists or not (see also VACZY and SCIPIADES, 1949).

e) The Ground Substance

of the endometrial stroma that bathes the cellular and fibrous components generally receives little attention, although it is particularly important in the processes of implantation (SCHMIDT-MATTHIESEN, 1962, 1963). During the normal menstrual cycle the ground substance seems to pass through three phases: in the early and mid-proliferative phase it chiefly contains high-molecular, neutral and acid mucopolysaccharides, which because of their metachromasia may be demonstrated with the Alcian-blue-PAS reaction (RUNGE *et al.*, 1956). In the late proliferative phase the ground substance begins to resolve into subgroups of low molecular size that elude histochemical analysis. During the first week of the secretory phase the stroma becomes looser; as the time for implantation approaches in the mid-secretory phase it becomes edematous. Directly thereafter, during the fourth week, high-molecular, neutral and acid mucopolysaccharides re-accumulate, but only in the compacta and about the spiral arterioles. These changes it seems make it easier for the blastocyst to implant and the trophoblast to invade and grow, since the ground substance is at its lowest viscosity and the stromal edema is at its peak. On the other hand, the increase in viscosity that occurs immediately after implantation promotes the adherence of the penetrating blastocyst. Closely integrated with all of these processes are the formation and disintegration of the reticulum fibers, the local release of relaxin, and the activation of fibrinolytic enzymes.

f) The Vessels

of the functionalis of the endometrium differ from vessels of other organs and tissues by their unique structure, their sensitivity to hormones and their ability to respond quickly to such stimuli (RAMSEY, 1955; NIEMINEN, 1962). In contrast, the vessels of the basalis are influenced little by hormonal changes of the cycle.

The *spiral arterioles* of the functionalis that branch from the arteries of the basalis finally attain the upper reaches of the endometrium at the end of the proliferative phase. Progesterone stimulates the vessels to grow larger and longer, hence leading to an increase in their tortuosity. Such changes are especially

evident during the second half of the secretory phase when the ratio of the height of the endometrium to the length of the spiral arteries is 1:15 (MARKEE, 1950). In other words, the arteries undergo intense spiralling because they grow faster than the endometrium. Their walls, thin in the early proliferative phase, grow progressively thicker (WIEGAND, 1930; FARRER-BROWN *et al.*, 1970). The lining endothelial cells, originally flat, swell and soon contain large, vesicular nuclei (KELLER, 1911). Electronmicroscopically they disclose a well-developed Golgi apparatus, abundant ergastoplasm, free ribosomes, mitochondria, and pinocytotic vesicles (ANCLA and DE BRUX, 1964). Ultimately the endometrial granulocytes aggregate to form broad mantles about the spiral arterioles. In addition to the changes induced by the humoral stimulation, the spiral arterioles located beneath the implanting blastocyst undergo marked hypertrophy. The endothelial cells of their most superficial and terminal portions (those branches of the precapillary arterioles nearest the trophoblast) proliferative intensely, piling up into several layers (WISLOCKI and STREETER, 1938; RAMSEY, 1949, 1955). Some investigators have explained these changes by postulating that hormones are acting locally (BORELL *et al.*, 1953). Several studies in animals indicate that the most likely hormone to cause these changes is relaxin, which owing to the fall in progesterone is released at this time from the endometrial granulocytes aggregated around the implantation site. By injecting monkeys with estrogen and relaxin, or by giving high doses of relaxin alone (DALLENBACH-HELLWEG *et al.*, 1966) we were able to induce a comparable hypertrophy of the spiral arterioles and intense proliferation of their endothelial cells (Fig. 9). Most probably the reason why the premenstrual release of relaxin fails to induce similar changes in the spiral arterioles is because the estrogen levels fall at that time or because the amount of relaxin available is much less than that released at the implantation site.

The *capillaries* of the functionalis also respond to cyclic variations of the ovarian hormones. The widely-branching, interstitial and periglandular capillaries extend through the compacta to pass just beneath the superficial epithelium. Their lumina, initially narrow, dilate irregularly during the secretory phase (BOHNEN, 1927; WILKIN, 1960; FANGER and BARKER, 1961), becoming largest in premenstrual endometria and particularly in young decidua of pregnancy. Often lacuna-like sinusoids form (the socalled "anastomosing lacuna" of SCHMIDT-MATTHIESEN, 1962). At the same time their endothelial cells become greatly swollen (KELLER, 1911; MAUTHNER, 1921; OKKELS, 1950).

The *veins* of the functionalis react to the hormonal stimuli of the secretory phase in like manner (KÜSTERMANN, 1930; BARTELMEZ, 1931; DEBIASI, 1962). The venous network in the endometrium is strikingly dense and in injection studies is much more prominent than the arterial vasculature. The main veins course downwards between the glands to enter the myometrium; they connect with each other however by numerous cross-anastomoses (FARRER-BROWN *et al.*, 1970). As OBER (1949) was able to show in serial sections, the thin-walled "lakes" beneath the superficial epithelium are merely localized sinusoidal dilatations of veins otherwise normally distended. Because of their extremely thin walls, these venous dilatations are difficult to distinguish from the lacuna-like sinusoids of the capillaries. Such a differentiation, however, would be of theoretical interest

only. On the other hand, the equally dilated, thin-walled vessels lined by several layers of proliferated endothelial cells are arterioles, as RAMSEY (1949) was able to prove in serial sections.

After menstruation, if the dilated vessels are not lost by desquamation, they rapidly shrink and revert to their original size.

Lymphatic capillaries end blindly just beneath the surface epithelium and the epithelial cells of glands. As the lymphatics descend to the basalis they merge to form collecting channels and lacunae, which run either parallel to the myometrium or penetrate it.

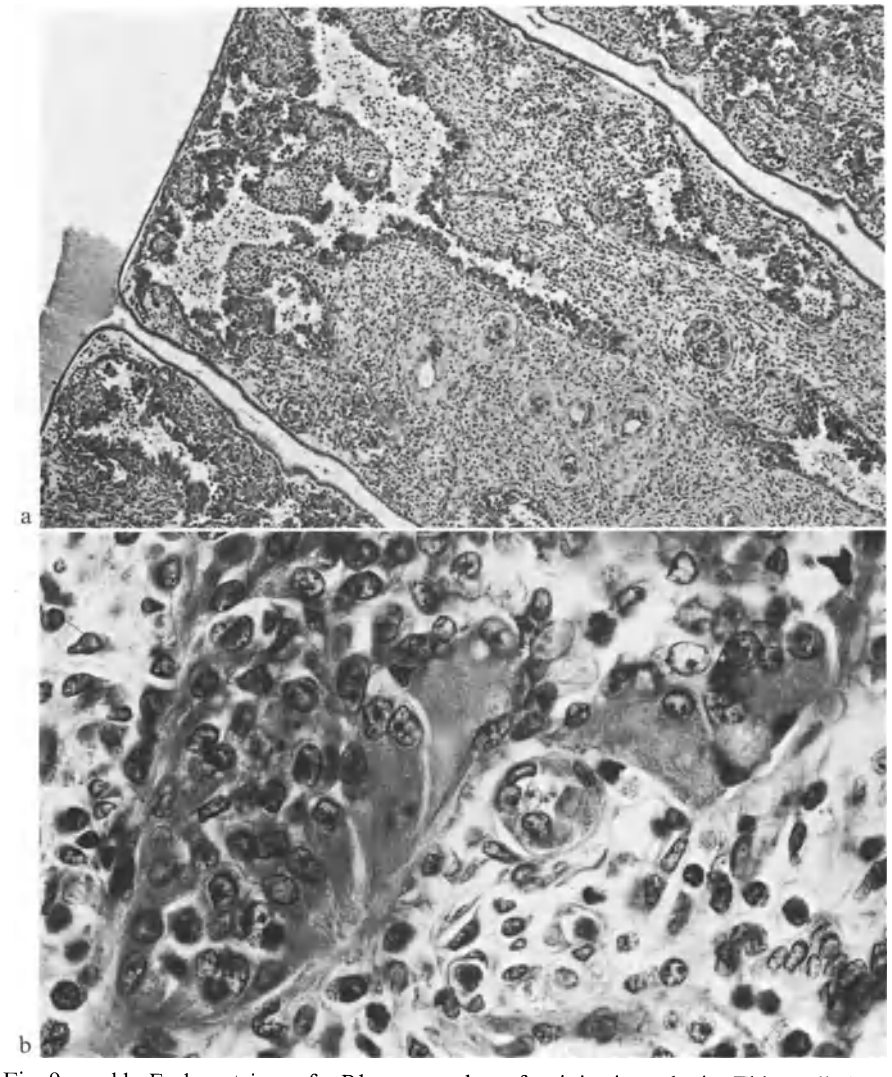


Fig. 9a and b. Endometrium of a Rhesus monkey after injecting relaxin. Thin-walled vessels in the compacta are dilated and the endothelial cells strikingly proliferated. (a) Low magnification. (b) Higher magnification

g) The Nerves

Despite intensive studies, opinions about the innervation of the endometrium until recently differed greatly. Some investigators reported finding branches of nerves in the basalis accompanying the arteries, and non-myelinated nerve fibers extending from these branches a short distance into the functionalis where they supposedly terminate about arterioles or glands (STATE and HIRSCH, 1941) or end free in the stroma (OKKELS, 1950; PRIBOR, 1951; KRANTZ, 1959). In contrast, KOPPEN (1950) was unable to demonstrate nerve fibers beyond the basalis although he searched for them. Using the osmium-zinc iodide method on the endometrium of the Rhesus monkey, LASSMANN (1965) reported seeing nerve fibers that extended to beneath the superficial epithelium where they ended with net-like fibrils. The fibers in his illustrations, however, appear more like those of the reticulum. Since the reticulum network of the endometrium is usually impregnated by all the techniques employed for demonstrating nerves, the positive results he reported should be evaluated with caution. Recently DALLENBACH and VONDERLIN (1973), by using new techniques, were able to demonstrate nerve fibers which extended into the endometrium to various levels, some as far as the functionalis. Where the nerve fibers ended remained unanswered since transected nerve fibrils proved to be too small to be recognized with the light microscopic methods they used. It seems improbable that nerve fibers, which might be lost during menstruation, could regenerate and reinnervate the newly formed functionalis during the relatively short proliferative phase. We may assume therefore that the level at which we find nerve fibers in the endometrium approximates the level at which shedding occurs during menstruation.

2. Histochemical Localization of Enzymes; the Reciprocal Action between Enzymes and Hormones

With the aid of histochemical methods, a large number of enzymes have been detected in the endometrium over the last thirty years. The activities of these enzymes are controlled in large part by hormones. On the other hand, the biological effects of the steroids depend in part on the enzyme systems of the endometrium, their "target organ" (FUHRMANN, 1961). The close interaction between hormones and enzymes in the endometrium takes on clinical significance, since demonstrating the presence or absence of an enzyme may permit valuable conclusions to be drawn about the functional state of the endometrium.

Some of the methods used for detecting enzymes are technically difficult and the results obtained are often equivocal owing to diffusion-artefacts. In addition, the numerous investigators of different laboratories have employed diverse methods on dissimilar material, making it difficult to evaluate or compare their results. I shall discuss here only those enzymes that are important in the diagnosis of the functional state. We shall confine ourselves to the results of histochemical studies of the human endometrium. Biochemical studies are not included. Further details may be obtained from comprehensive reviews (BONTKE, 1960; SCHMIDT-MATTHIESEN, 1963).

Of all the enzymes, the activity of **alkaline phosphatase** has been studied the most. Since the results of the studies have consistently agreed, we can assume

they are reliable. The activity is greatest during the proliferative phase, reaches its peak shortly before or at ovulation, then rapidly falls in the secretory phase to minimal levels (ATKINSON and ENGLE, 1947; ANDRES *et al.*, 1949; ATKINSON, 1950; HALL, 1950; OBER, 1950; WISLOCKI *et al.*, 1950; RUNGE and EBNER, 1954; MCKAY *et al.*, 1956; BERGER and MUMPRECHT, 1959; BARBOUR, 1961; FUHRMANN, 1961; LEWIN, 1961; MOOKERJEA, 1961; BOUTSELIS *et al.*, 1963; GROSS, 1964; KUCERA, 1964; SAKSENA *et al.*, 1965; TAKI *et al.*, 1966; FILIPE and DAWSON, 1968). As judged from the precipitation-reaction that takes place in the test, the enzyme is localized primarily at the apical end of the glandular epithelial cell. During glycogenolysis the cell membrane becomes more permeable (HUGHES, 1976). In the stroma only the vascular endothelium gives a positive reaction. Apparently the activity of alkaline phosphatase is closely associated with the action of estrogen on the endometrium. Although biochemically different from alkaline phosphatases of other organs (WILSON, 1976), it most probably is also important for protein synthesis and in the associated processes of growth and prolifertion. It possibly particiates in the formation of mucoids (SCHMIDT-MATTHIESEN, 1963), enhancing cell membrane permeability at the time of glycogenolysis.

The large number of **lysosomal enzymes** in the endometrium increase their activities up to and during the secretory phase when the lysosomal membranes begin to become destabilized, leading to either a gradual or a drastic increase in free, non-lysosomal bound enzymes (ROSADO *et al.*, 1977). Apparently the important mechanism regulating the number of these lysosmal enzymes and the stability of their membranes is the appropriate equilibrium between estrogens and progesterone.

The histochemical reactions for demonstrating *acid phosphatase* are technically complicated; therefore we should expect they would occasionally yield erroneous results. According to the reports of most investigators, the activity of the acid phosphatase during the menstrual cycle reacts just the opposite of that of alkaline phosphatase. Its activity during the proliferative phase is very low but rises continuously after cycle day 21 to reach its peak just before menstruation (ANDRES *et al.*, 1949; GOLDENBERG and JONES, 1956; MCKAY *et al.*, 1956; FUHRMANN, 1961; MOOKERJEA, 1961; BOUTSELIS *et al.*, 1963; VACEK, 1965; SAWARAGI and WYNN, 1969). Some investigators found the peak of activity at the time of ovulation (BERGER and MUMPRECHT, 1959; GARCIA-BUNUEL and BRANDES, 1966). Others were unable to detect obvious differences between the proliferative phase and the secretory phase (WISLOCKI *et al.*, 1950; GROSS, 1964; BITENSKY and COHEN, 1965; FILIPE and DAWSON, 1968; BARON and ESTERLY, 1975). Acid phosphatase is primarily localized in the cytoplasm of the glandular epithelium. In addition, some stromal cells usually give a positive reaction. GOLDBERG and JONES (1956) and VACEK (1965), however, reported a premenstrual increase in the activity in cells they called macrophages. In studies on the permeability of lysosomal membranes, BITENSKI and COHEN (1965) were able to demonstrate that acid phosphatase in the endometrium was located in the lysosomes. The reaction for the enzyme was positive only with permeable membranes. Since progesterone affects the permeability of lysosomal membranes, it is easy to understand that the activity of acid phosphatase might depend on the level of progesterone.

Glucose-6-phosphatase can be localized ultrastructurally within cisterna of the endoplasmic reticulum and in the nuclear membrane of glandular epithelial cells around the time of ovulation and during the early secretory phase (SAWARAGI and WYNN, 1969). It apparently converts the large amounts of glycogen produced at that time into glucose.

Specific and non-specific *esterases* behave very much like acid phosphatase and like it are localized in lysosomes. GROSS (1964), VACEK (1965) and MANSOUR and BARADI (1967) found an increase in the activity in the secretory phase, whereas NACHLAS and SELIGMAN (1949), MCKAY *et al.* (1956), BOUTSELIS *et al.* (1963), GARCIA-BUNUEL and BRANDES (1969), and TAKI *et al.* (1966) were unable to detect any significant variations during the menstrual cycle. In the late secretory phase, however, these authors found a high activity of esterase in stromal "macrophages", which JIRASEK and DYKOVA (1964) were able to prove were actually endometrial granulocytes. In my own studies I have been able to confirm that endometrial granulocytes contain esterases and acid phosphatase. Since relaxin begins to exert its effect when progesterone falls, the release of relaxin seems to be closely associated with the increase in activity of the esterases and acid phosphatase, or rather, with the permeability of the lysosomal membranes (cf. p. 28).

Proteolytic enzymes also occur in the endometrium. *Aminopeptidase,* however, is the only one that has been studied histochemically (FUHRMANN, 1959; FILIPE and DAWSON, 1968; BARON and ESTERLY, 1975). Its activity increases during the menstrual cycle and is greater in the stromal cells than in the glandular epithelial cells.

Using biochemical methods, SCHMIDT-MATTHIESEN (1967) studied some other proteolytic enzymes (the fibrinolysokinases and tryptases), which he extracted from endometrial tissue along with such active agents as plasminogen, plasmin, and other activators of fibrinolysis. He referred to the combined effect of these enzymes and agents as the "fibrinolytic activity" of the endometrium. He found that the activity reaches its peak during mid secretory phase. If pregnancy ensues, then the activity falls. Just before menstruation it rises again, attaining a second peak on the first day of menstruation (RYBO, 1968). The administration of estrogen causes the activity to increase; progesterone causes it to decrease. In contrast, intact decidua and placenta reveal no fibrinolytic activity. Attempts to localize the fibrinolytic enzymes histochemically indicate they are probably confined to the intima of small arteries, capillaries and venules, and to the stromal cells about the glands of the superficial endometrium (WEISS and BELLER, 1969). Also a possible source of fibrinolytic enzymes is the endometrial granulocytes, which most likely retain the enzymes in lysosomes (HENZL *et al.,* 1972). Some of these enzymatic activators contain lipids; accordingly, most are bound to microsomal fractions. The fibrinolytic enzymes become effective only after they are released from the cell. Their liberation appears to be induced by hormonal conditions like those that are necessary for the release of relaxin. Perhaps, however, pathological changes in hormonal balance also cause the cells to liberate their fibrinolytic activators. In contrast, the acid mucopolysaccharides that appear in the ground substance during the early proliferative and late secretory phases can act as fibrinolytic inhibitors by binding with the fibrinolytic enzymes to form complexes.

From all that we have said, it appears that the fibrinolytic activity of the endometrium is closely related to the release and action of relaxin; the relationship is not only functional but morphological as well.

Some other lysosomal enzymes that have been histochemically demonstrated should be briefly mentioned:

β-glucuronidase has its peak of activity in all probability during the secretory phase (GROSS, 1964; VACEK, 1965). Other authors found, however, that the enzyme showed no important fluctuations during the menstrual cycle (FUHRMANN, 1961; BOUTSELIS *et al.,* 1963; TAKI *et al.,* 1966; FILIPE and DAWSON, 1968). Although β-glucuronidase is chiefly present in the glandular epithelium, small amounts of the enzyme are also found in some stromal cells. Apparently it is important in the metabolism of carbohydrates. *Phosphoamidase* reaches its greatest activity in the glandular cells of the endometrium during the first half of the secretory phase (OEHLERT *et al.,* 1954; GROSS, 1964). BARON and ESTERLEY (1975) reported that the activities of *galactosidase* and *glucosaminidase* peak in the late secretory phase.

A group of other enzymes are important in the metabolism of carbohydrates. *Glycogen-synthetase* activates the synthesis of glycogen from glucose. *Glycogen-phosphorylase* catalyzes it back to glucose. Both enzymes have their greatest activities in the secretory phase. *Glucose-6-phosphatase* can be localized electron-microscopically in the cisternae of the endoplasmic reticulum and in the nuclear membrane of glandular epithelial cells at ovulation and during the early secretory phase (SAWARAGI and WYNN, 1969). It also participates in the breakdown of glycogen into glucose.

The few studies of the *dehydrogenases* indicate some of these enzymes probably fluctuate very little during the menstrual cycle (FORAKER *et al.,* 1954; MARCUSE, 1957; COHEN *et al.,* 1964; VACEK, 1965; LUH and BRANDAU, 1967). Recent studies on the histochemical localization of 17 β- and 3α-hydroxysteroid-dehydrogenases showed almost no activity of these enzymes during the proliferative phase of the menstrual cycle, but distinct activity during the secretory phase with a maximum around the 22nd day. The enzymes were mainly localized in the apical end of the glandular cells, and here within the outer membranes of the mitochondria and in microsomes (POLLOW *et al.,* 1975). Stromal cells showed no activity. The prime function of these two enzymes, particularly the 17β-hydroxysteroid-dehydrogenase, seems to be to stimulate the secretory activity of the glandular cell by steroid oxidation (BRANDAU *et al.,* 1969). *Carbonic anhydrase,* primarily localized at the base of the glandular epithelial cells during the entire cycle, appears to be important in processes of implantation (FRIEDLEY and ROSEN, 1975).

3. Structural Changes Induced in the Endometrium by the Physiological Action of the Ovarian Hormones

a) Molecular Biology of Steroid Hormones

The rapid and great advances in the molecular biology of steroid hormones during the last decade have made this subspecialty a particularly exciting

discipline of endocrinology. As one might guess, the wealth of new information gained virtually defies adequate summary, especially in these few paragraphs. For details I refer the interested reader to comprehensive treaties covering various aspects of the subject, many of which remain controversial or unclear (JENSEN *et al.,* 1969; MAINWARING, 1975, 1977; CHAN and O'MALLEY, 1978; SCHRADER and O'MALLEY, 1978; JENSEN, 1979; MARKS, 1979).

Since steroid hormones have molecular weights of about 300, they can readily diffuse into all cells of the body, but as we know, they trigger characteristic reactions only in cells of their target tissues. As tritiated steroids in radioautographic, affinity chromatographic, cell fractionation and gradient centrifugation studies have revealed, the high affinity of these target tissues for a steroid comes from the capacity of their cells to produce special cytoplasmic proteins, which specifically and rapidly intercept and bind the hormone as it diffuses into the cell. Because of that "welcoming" function, the cytoplasmic protein has been named a "receptor". To be able to respond to a steroid hormone, a target cell must produce receptors specific for that hormone. Consequently, receptor proteins specific for estrogens or progesterone, or androgens, or glucocorticosteroids or mineralcorticosteroids have been identified.

The receptors actually have two functions (BAXTER and FUNDER, 1979). The first is to recognize and select out of the hodgepodge of hormones in the fluid bathing the cell the appropriate hormone as a signal. The second is to relay that signal to the nucleus where it specifically effects the genome bringing about definite changes in the cell. Most investigators assume that all steroid hormones act alike. GORSKI and JANNON (1976), however, present data detailing differences that exist between different steroid hormones. They explain in detail why they believe the differences should be considered. Steroids of lower biological activity, such as estrone and estriol, seem to have lower affinities for receptors (BAULIEU *et al.,* 1980).

Because receptor proteins are difficult to purify before they become denatured, various investigators have described at least eight different subunits for the estrogen receptor. SICA and BRESCIANI (1979) have reported the molecular weight of the denatured subunit of estrogen to be close to 70,000 daltons. Each subunit has one binding site for estrogen. O'MALLEY and SCHRADER (1976) estimate the molecular weight of the progesterone receptor to be about 200,000. They describe it as a dimer of two unlike subunits. Each weighs about 100,000 and consists of a cigar-shaped chain of aminoacids four to five times as long as it is wide, providing one binding site for progesterone. Nonetheless, as GORSKI and GANNON emphasize, depending on the techniques used to collect them from the cytosol of the target cells, complexes of steroid hormones with receptors may have a variety of forms and molecular weights. BAULIEU *et al.* (1980) thoroughly review the many problems associated with measuring the properties of receptors bound to radioactive hormones.

Most cells of a target organ maintain about 10,000 such steroid receptors in their cytoplasm. GORSKI and GANNON (1976) estimate about 16,000 receptors per cell. The number may fluctuate, however, depending on the intensity and duration of prior hormonal stimulation, on the degree of cellular differentiation,

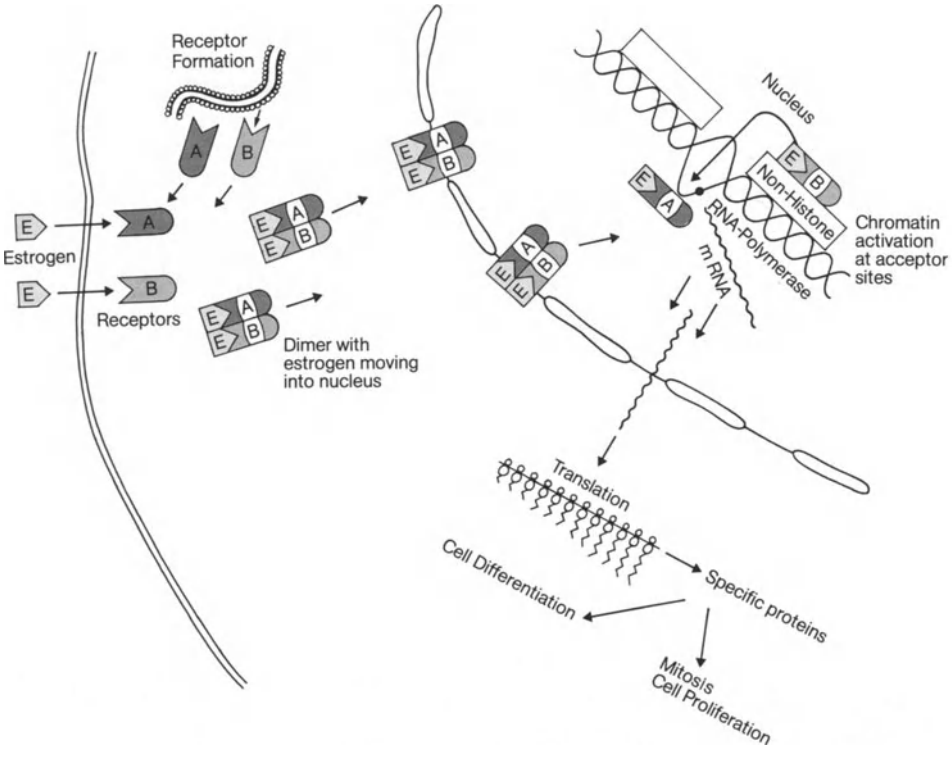


Fig. 10. Schematic portrayal of how steroid hormones (estrogen here) seem to bind to receptors at plasma membrane to be carried into nucleus where they activate specific "acceptor" sites and genes to induce transcription, then translation, with either cell differentiation or cell proliferation (for details see text)

and such factors as phase of cell cycle, cell age, metabolism, genetic state (SIBLEY and TOMKINS 1974; GEHRING *et al.*, 1971; KIRKPATRICK *et al.*, 1971), nutrition, pharmacologic pretreatment, effects of other hormones, pathologic states, and so on. For example, a hormone (agonist) may depress the levels of its own receptors, a process known as "down-regulation" or tachyphylaxis (BAXTER and FUNDER, 1979). This may explain in part why large doses of estrogen over long periods may lead to ultimate failure of its target cells to respond. According to MILGROM *et al.* (1973), progesterone seems to inactivate its own receptor system. On the other hand, a hormone such as estrogen is known to increase the levels of receptors for progesterone and prolactin (LEAVITT *et al.*, 1977). In contrast, progesterone may depress the level of estrogen receptors, making the target tissue less sensitive to estrogen (MESTER *et al.*, 1974; HSUEH *et al.*, 1975). Whether estrogens under certain physiologic conditions can bind to more than its class of receptors, as spirolactone does to androgen receptors (FUNDER *et al.*, 1976), or whether other non-estrogenic hormones can bind readily to estrogen receptors, is not known. BAXTER and FUNDER (1979)

recommend one should take such "overlap" in action into account when hormone therapy is considered, and ROCHEFORT and GARCIA (1976) reported the binding of androgens to the estrogen receptor can bring about an estrogenic effect.

Although its affinity for the estrogen receptor is relatively low, Tamoxifen acts as a powerful anti-estrogen because it is so slowly metabolized and lingers at high concentrations in the cytoplasm competing with estrogens.

As recent studies indicate (BAXTER and FUNDER, 1979; BAULIEU, 1979), when a given steroid fails to stimulate its target tissues, it is usually because the tissues lack receptors for that hormone.

The affinity of a hormone for a receptor involves electrostatic forces, whereby hydrogen bonds unite charged groups on the hormone with oppositely charged groups on the socalled binding site of the receptor. These processes are dependent on temperature. All facts suggest the receptor changes its shape and its molecular weight (referred to as "conformational change") whereby it becomes activated, enabling it to slip through nuclear pores, to enter the nucleus where it signals specific changes (Fig. 10). The process of translocation from cytoplasm to nucleus proceeds quickly but apparently requires no energy. Perhaps it represents, as some suggest, nothing more than a flow initiated by gradient differences.

On arrival in the nucleus the hormone receptor complex interacts and binds with high affinity to socalled "acceptor" sites on the chromatin, inducing thereby changes in numerous gene loci (GORSKI and GANNON, 1976; YAMAMOTO and ALBERTS, 1976; BAULIEU, 1979; BAULIEU et al., 1979). For the estrogen receptor complex there seems to be more acceptor sites than receptors, thus the nuclear binding sites never become saturated. Whether the acceptor sites for the progesterone receptor complexes also outnumber the progesterone receptors is not known but seems probable.

O'MALLEY and SCHRADER (1976) review the results of their studies with progesterone and explain how they believe the subunits A and B of the dimeric progesterone receptor bind at different but specific acceptor sites on the chromatin to activate genes. It remains to be proved whether their hypothesis applies to all steroid hormones.

As these investigators postulate, when the progesterone receptor complex enters the nucleus the B subunits bind to a specific acceptor protein on the chromatin, where a special AP_3 fraction of the non-histone chromosomal proteins is located. The other subunits A, unable to bind to intact chromatin, dissociate from the B subunits and react with specific genes situated nearby on the chain of naked DNA. The choice of specific genes is presumably determined by the B subunits as they bind with the AP_3 fraction or some protein of it. The reaction of the subunits A with the specific genes attracts a molecule of RNA polymerase to the site to initiate a locus for DNA transcription. Accordingly, strands of messenger RNA are transcribed and move off into the cytoplasm to serve as templates for protein synthesis, bringing about changes in cell structure and function we recognize histologically as characteristic of that hormone. In part this hypothesis agrees with that of YAMAMOTO and ALBERTS (1976) for estradiol. Yet attempts to purify estrogen receptor have not

led to the isolation of two binding forms as with progesterone, nor has the estrogen receptor revealed a specific binding to a single AP_3 acidic non histone protein of chromatin.

The number of chromatin acceptor sites exceed the number of messenger RNAs stimulated by the steroid hormone. That suggests receptor-steroid complexes may be bound to sites which serve other supportive functions of less physiologic importance. Only about 1% of the messenger RNA's in the cell are regulated by the steroid hormone.

What happens to the steroid after it partakes in gene stimulation, whether it is destroyed or extruded from the cell, little is known. In vivo estradiol has a half life of about 90 minutes. What the fate of the hormone receptor is remains unknown. It may be deactivated, returned to the cytoplasm for reuse, or may be destroyed by proteolysis. BAULIEU (1979) states that in humans under normal conditions, the steroid concentrations never saturate all binding sites on the cytoplasmic and nuclear receptors.

b) Endometrial Steroid Receptors

Studies to date indicate that the receptors for estrogen and progesterone in the endometrium fluctuate during the menstrual cycle and may determine when the fertilized ovum will implant (BAYARD *et al.*, 1978; BAULIEU *et al.*, 1979; SOUTTER *et al.*, 1979). LUNAN and GREEN (1975) were able to confirm earlier results showing that endometrium from various parts of the uterus yielded differences in uptake of estradiol, especially in the secretory phase, proving it is unwise to assume that all samples of endometrium taken from a single uterus will yield like values for estrogen receptors. They suggested the differences might be related to variations in vascular supply or to variations in distribution of endogenous hormones.

In *the early proliferative phase*, estradiol receptors gradually increase. The progesterone receptors are only slightly less. In the *late proliferative phase* the concentration of total estradiol receptors increases. Those of the nucleus more than double, whereas those of the cytoplasm remain unchanged. The cytoplasmic progesterone receptors increase greatly, correlating with the surge of plasma estradiol.

After ovulation, the total estradiol receptor decreases rapidly in the early secretory phase, mostly through a fall in cytoplasmic receptors, and continues to decrease in the late secretory phase, reaching levels well below those at the onset of the cycle. The total concentration of progesterone receptors gradually falls, with a sharp decrease in cytoplasmic receptors. The nuclear receptors remain at their highest levels, correlating well with the luteal secretion of progesterone. In the late secretory phase the concentration of nuclear receptors falls to values of the early proliferative phase.

During first trimester of pregnancy, the cytoplasmic estradiol and progesterone receptors are barely detectable whereas progesterone nuclear receptors are high, exceeding concentrations of total progesterone receptors of preovulatory endo-

metrium. The concentrations of estradiol nuclear receptors resemble those of the early secretory phase.

c) Estrogen

In contrast to other steroid hormones, minute amounts of estrogen (17β-estradiol) are very potent, capable of producing rapid and significant changes in the target cells.

Within 15–30 minutes after estradiol is administered, the rate of nucleotide uptake by the endometrial cells rises and the RNA of their nuclei markedly increases (SEGAL, 1967). A shift of the nucleoli to the nuclear membrane takes place (RICKERS and KRONE, 1969). Between one and two hours after giving estradiol the amounts of glycogen, phospholipid and fluid in the uterine cells sharply rise. Shortly thereafter the cells begin to synthesize protein, and cell growth ensues (HAMILTON, 1964); at the same time the activity of alkaline phosphatase and adenosine triphosphatase increases (HENZL *et al.*, 1968). Estradiol remains in the nuclei of "target cells" for many hours, stimulating the synthesis of DNA (KING and GORDON, 1967; LEROY *et al.*, 1967; STUMPF, 1970); the result is a wave of mitoses. In the endometrium both the stromal cells and epithelial cells briskly respond. EPIFANOVA (1966), who injected mice with estrone, found the mitotic index of the uterine epithelium to be increased by a factor of 4.5.

The prompt hyperemia of the endometrium, occuring within one minute after intravenous injection of estradiol, and the subsequent rapid uptake of water were often regarded as responses to estrogen. We now realize these changes are mediated by histamine that is released locally by estrogen; how estrogen sets histamine free, however, is unknown.

In summary, estrogen regulates the amount of genetic material available for transcription and helps to control the chemical composition of the genetic material (VILLEE, 1961; JENSEN, 1963; KARLSON, 1965, 1967; TENG and HAMILTON, 1968).

Of special interest are the studies of KOHRMAN and GREENBERG (1968) who, confirming and elaborating on the results of other investigators, showed that a single injection of estradiol into neonatal mice produced changes in the vaginal epithelium that persisted long into adult life. Not only did the vaginal cells persistently proliferate and hornify, but the rates of synthesis of DNA, RNA and protein of these target cells remained permanently altered. The mice that DUNN and GREEN (1963) studied after similar neonatal injection ultimately developed cervical carcinomas.

The first morphological and histochemical effects of estrogen that we can see in the glandular and stromal cells of the human endometrium are the increase in RNA in the nuclei and nucleoli, followed by increase in cytoplasmic RNA. Thereafter, the synthesis of cytoplasmic protein accelerates, leading to growth and proliferation of the cells (DAVIDSON, 1965; POTTER, 1965; PODVOLL and GOODMAN, 1967). At the same time we find the activity of alkaline phosphatase rises. As its cells enlarge, its glands grow longer, and its stromal cells proliferate, the endometrium increases in height. Many of the epithelial and stromal cells may be found undergoing mitosis. The more the endometrium grows, the more estrogen the ovaries secrete, adapting it seems to the steady increase in endometrial

tissue. Finally with the secretion of progesterone, the endometrial cells cease to proliferate.

d) Progesterone

As explained above under molecular biology of steroid action, specific receptors for progesterone have been detected in the endometrium. (EDWARDS *et al.*, 1969; RAO and WIEST, 1970; TRAMS *et al.*, 1971; RAO *et al.*, 1974). The progesterone binding increases quantitatively after pretreatment of castrate animals with estradiol-17β (RAO *et al.*, 1973).

In the test named after them, HOOKER and FORBES (1947) determined the smallest dose of progesterone that corrects the changes induced in the endometrial cells of the mouse by castration: After 0.0002 µg of progesterone are injected within the uterine cavity, the nuclei of the endometrial stromal cells enlarge and become clear after two days. If the dose of progesterone is doubled, then the nuclei "revert to normal" within twenty-four hours; with a fourfold dose, the reversion occurs within six hours. The effect is specific for progesterone, given by no other hormone. Cytophotometric measurements have disclosed (LEROY *et al.*, 1967) that as the nuclei enlarge the DNA increases 20 per cent.

In human endometrium the first evidence of a progesterone effect is detectable with the light microscope after thirty-six hours; one sees a clearing of the nuclei of the glandular and stromal cells and glycogen granules begin to appear at the base of the glandular epithelial cells. Before these changes can occur, however, the cells must have been stimulated by estrogen as in a normal menstrual cycle (HUGHES *et al.*, 1969). During organ culture in media containing progesterone, the glycogen content of proliferative tissue was increased as much as thirteenfold (SHAPIRO *et al.*, 1980). In electron-microscopic studies MERKER *et al.* (1968) found giant mitochondria containing DNA near the glycogen granules; these investigators postulated that progesterone stimulates these mitochondria to synthesize protein. Later in the menstrual cycle under the effects of progesterone, a nuclear channel system develops (see p. 23). Mitotic activity ceases, and the amount of alkaline phosphatase decreases; the glandular cells differentiate. In addition to glycogen, they produce and secrete neutral and acid mucopolysaccharides and lipids. In the second week of the secretory phase the stromal cells differentiate either into large predecidual cells or into small endometrial granulocytes; the spiral arterioles begin to grow. The activity of acid phosphatase rises.

e) Relaxin

HISAW in 1926 discovered this hormone and described its action on the symphysis pubis of the guinea pig. He defined the guinea pig unit (GPU) of relaxin as the smallest dose to cause in six hours a widening of the symphysis pubis in 66 per cent of castrated female guinea pigs pretreated with estrogen. In sexually mature monkeys the levels of relaxin in the blood fluctuate between 0.2 and 0.3 GPU/ml serum (HISAW and HISAW, 1964). At the beginning of pregnancy women average about 0.2 GPU/ml, but at the end of pregnancy about 2 GPU/ml (ZARROW *et al.*, 1955). Recent observations, however, rather showed a slight decline in plasma concentrations toward the end of gestation (SCHWABE *et al.*, 1978). Nonpregnant women can produce relaxin when given HCG (QUAGLI-

ARELLO *et al.*, 1980). Mammals with a primitive placentation produce the hormone primarily in the ovary (as in pigs), but in women (DALLENBACH and DALLENBACH-HELLWEG, 1964) and in monkeys (DALLENBACH-HELLWEG *et al.*, 1966) the hormone or its precursor seems also to be formed by the granulocytes of the endometrial stroma. Granules resembling those of endometrial granulocytes have been found in granulosa lutein cells of porcine (BELT *et al.*, 1971; KENDALL *et al.*, 1978) and human (CRISP *et al.*, 1970) ovaries. The occurrence of these granules also correlates with relaxin production. The lysosomes found near to the granules in the endometrial and ovarian cells suggest that enzymes may activate precursor prorelaxin to relaxin, which then acts only at definite times in specific tissues; the stimulus inducing the release of lysosomal enzymes and of relaxin is the fall of progesterone.

As recent studies have disclosed, relaxin is a polypeptide hormone of 5447 molecular weight with an A chain of 22 amino acids and a B chain of 26 amino acids connected by disulfide bridges much like insulin. Consequently, the specifity of earlier observations made with labelled antibodies directed against relatively impure relaxin should be tested and proved by using the pure relaxin now available. Recently with this substance relaxin was demonstrated in human decidua and placenta at term (BIGAZZI *et al.*, 1980). As yet no receptor specific for relaxin has been detected.

During the last days of the normal secretory phase, relaxin stimulates dilatation and congestion of the thin-walled capillaries located just beneath the surface epithelium (those that communicate with the "anastomosing lacuna"), and induces dissolution of the reticulum fibers of the endometrial stroma. That dissolution, in turn, allows the stromal cells to dissociate, facilitating menstrual shedding (Fig. 8). A similar disintegration of the connective tissue takes place at the onset of implantation, but only about the embedding blastula. The much larger amounts of relaxin released at the end of pregnancy or with an abortion stimulate profound dilatation of the thin-walled capillaries and extreme hyperplasia of their endothelial cells, as well as of those of the spiral arterioles. Further, immediately after birth relaxin causes the fibers of connective tissue that hold the placenta in place to undergo dissolution. These actions of relaxin have been confirmed in monkeys by injecting them with relaxin (DALLENBACH-HELLWEG and DALLENBACH, 1966; Fig. 9). The dissolution of collagen fibers could be verified in electron-microscopic observations (CARDELL *et al.*, 1969). In addition to these local effects of relaxin that may be brought about in part by intermediary systems of enzymes, there are the distant effects of relaxin on the cervix and symphysis pubis. These distant effects are also controlled to take place at definite times; since they are not pertinent they shall not be discussed further.

4. Changes in Structures in the Endometrium During Nidation

Although we described earlier how the various structures of the endometrium change with the advent of pregnancy, we shall review these changes here in detail. As emphasized before, virtually every structural component of the endometrium takes part in preparing for implantation. That would seem to provide multiple assurances to guarantee success of the processes involved. On the other hand, it is essential that the intricate interplay between tissue components, so

carefully regulated by the delicate balance of hormones, is precisely maintained to insure a normal implantation. Knowledge of all of the tissue components and their changes gives us insight into the diversity of possible causes for sterility.

At the time of implantation on the seventh day after ovulation the endometrial glands are at their height of secretion. The endometrial stroma is maximally edematous, its fibers loosely dispersed, and its ground substance watery and rich in depolymerized substances that are more easily absorbed because of their reduced molecular sizes. The fibrinolytic activity is at its peak. The spiral arterioles proliferate and hypertrophy, finally reaching the upper compacta just beneath the surface epithelium. In women (as in other mammalian species) the blastocyst implants directly over a group of these spiral arterioles, and as it does so it apparently stimulates the adjoining endometrium to undergo profound structural changes. The group of spiral arterioles beneath the lower pole of the imbedding blastocyst responds by intense hypertrophy, and in the surrounding stroma the capillaries widely dilate and their walls become thin. Large, "true" decidual cells develop. These possess "gap" junctions that connect processes from the same cell but fail to show similar junctions with neighboring cells as predecidual cells do (LAWN *et al.*, 1971). The granulocytes increase in numbers; those that have assembled about the implanting blastocyst release their relaxin, most probably owing to a local deficit of progesterone (or to an estrogen excess). The liberated relaxin causes the reticulum fibers locally to disintegrate. In addition, probably because of the same hormonal stimulus, the fibrinolytic activity reaches its peak and proteolytic enzymes are set free in the same region. Perhaps it is the hormonal activation of lysosomal enzymes that finally brings about the release of the relaxin. The blastocyst readily penetrates the region where the reticulum fibers have disintegrated, and becomes firmly imbedded after establishing contacts with the maternal blood vessels. Thereafter, the surrounding decidua develops, serving to limit further spread of the trophoblast. Over the next few days the hormones secreted by the corpus luteum of pregnancy cause the endometrium to grow even higher. The reticulum fibers become denser, the ground substance turns more viscid, and the blood vessels proliferate and dilate. As a result, the decidua that surrounds the imbedding blastocyst becomes established and stable. Its granulocytes accumulate their relaxin for use later in the frequent, local processes of destruction and remodeling, which characterize the fluctuating state of the decidua throughout pregnancy. Thus we see, contrary to earlier opinion, that the endometrium participates in the process of implantation, not only by providing little resistance for the blastocyst, but particularly by taking an active part in the dissolution of its reticulum fibers, as long as that is essential for implantation. In addition, through their decidualization about the blastocyst, the endometrial cells help to anchor it in place. Thereby, as electron-microscopic studies show, the contact between decidual cells and trophoblasts becomes close (TEKELIOGLU-UYSAL *et al.*, 1975). In contrast, the decidualization of the more distant endometrium about the implantation site remains less differentiated during the entire period of gestation (ARRONET *et al.*, 1973).

In addition to the morphological changes as sketched here, numerous biochemical alterations also take place (STRAUSS, 1964; SCHMIDT-MATTHIESEN, 1968; EDWARDS and SURANI, 1978; LEROY, 1980; BEIER, 1981). In this brief review,

however, it is impractical and impossible to cover all aspects of the entire, complex process of implantation. Animal experiments of the last few years have brought us some information (cf. NILSSON *et al.*, 1978; BÖVING, 1964; WYNN, 1967; FRIDHANDLER, 1968) but the field is still much in flux; many questions remain unanswered.

5. The Endometrium before Puberty

In *fetal* endometrium isolated invaginations of epithelium begin to form glands by the fifth month, and the epithelial cells begin to grow taller. By the eighth month the cells are columnar, contain basal glycogen vacuoles, and discharge some secretions into the glandular lumen (KAISER, 1963; HUBER *et al.*, 1971). Although the fetal endometrium is acted upon by estrogen and progesterone from the beginning, its development is that of a pure estrogen effect. Only after reaching a certain stage of maturity in the eighth month does the endometrium respond to progesterone. The tortuosity of the glands increases until birth. The nuclei of the epithelial cells become rounded; the cytoplasm shows activity of alkaline and acid phosphatases (PRYSE-DAVIES and DEWHURST, 1971). The dense stroma of small cells becomes loose, the nuclei increase in size (HIERSCHE and MEINEN, 1971), and occasional predecidual cells may be seen.

Because of the hormonal effects on it during pregnancy, the endometrium of baby girls is still hyperplastic at birth. In 169 *newborns,* OBER and BERNSTEIN (1955) found that 68 per cent had a proliferative endometrium, 27 per cent had a secretory endometrium, and 5 per cent had an endometrium with predecidual change or early signs of menstrual shedding. Within fourteen days after birth, however, the endometrium regresses to a height of at most 0.4 mm; its short glands are sparse, embedded in a delicate stroma of spindly cells. The surface epithelium is low.

With the onset of *puberty* the endometrium begins to proliferate again. After the mucosa builds up under the influence of estrogen, cyclic changes then gradually set in. Since the hemorrhages that soon follow are anovulatory, secretory changes in the endometrium are absent for the time.

6. The Normal Menstrual Cycle and Its Possible Variations

Here we shall examine in detail the histological changes induced in the endometrium by the ovarian hormones from day to day during a normal cycle. A thorough knowledge of these changes is a prerequisite for making accurate functional diagnoses of curettings (Fig. 11 a).

After the first histological description of the cyclic changes of the endometrium by HITSCHMAN and ADLER (1908), numerous supplementary reports followed (SCHRÖDER, 1913, 1915, 1928; O'LEARY, 1929; BARTELMEZ, 1933; HERRELL and BRODERS, 1935; ROCK and BARTLETT, 1937; FALCONER, 1948; and many more). The results of these studies and the information learned about the function of hormones helped to clarify notions of the menstrual cycle. We are most indebted to NOYES *et al.* (1950), however, for the first detailed description on how "to

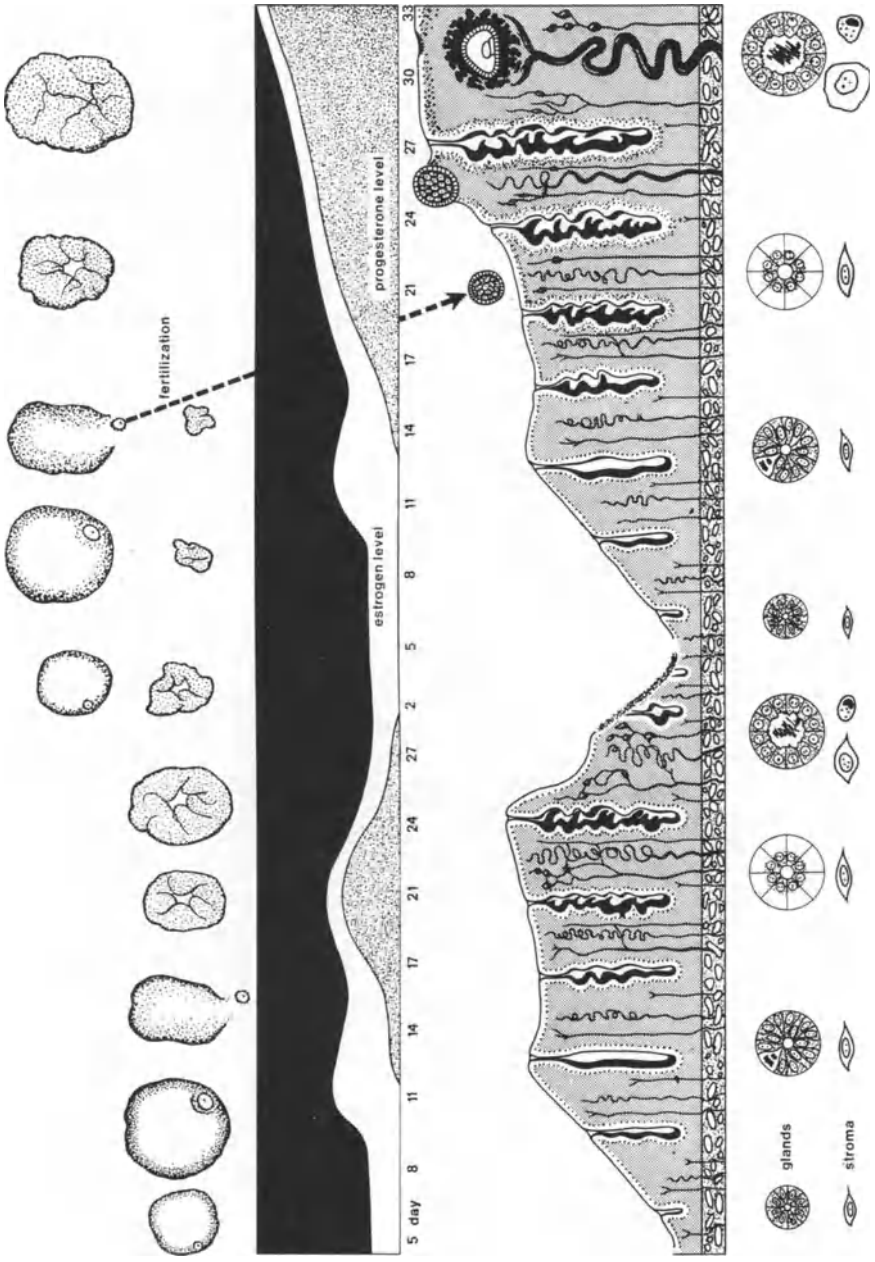


Fig. 11a. Menstrual cycle and implantation as controlled by ovarian hormones

date the endometrium" from histological criteria; that is, on how to diagnose how far an endometrium has developed in the menstrual cycle from characteristic histological changes that are known to occur at specific times (Fig. 11 b). MORICARD (1954) and PHILIPPE *et al.* (1965) confirmed the data of NOYES *et al.*

Recent advances in hormone therapy in gynecology have required that we attempt to learn how estrogen and progesterone act on the endometrium under

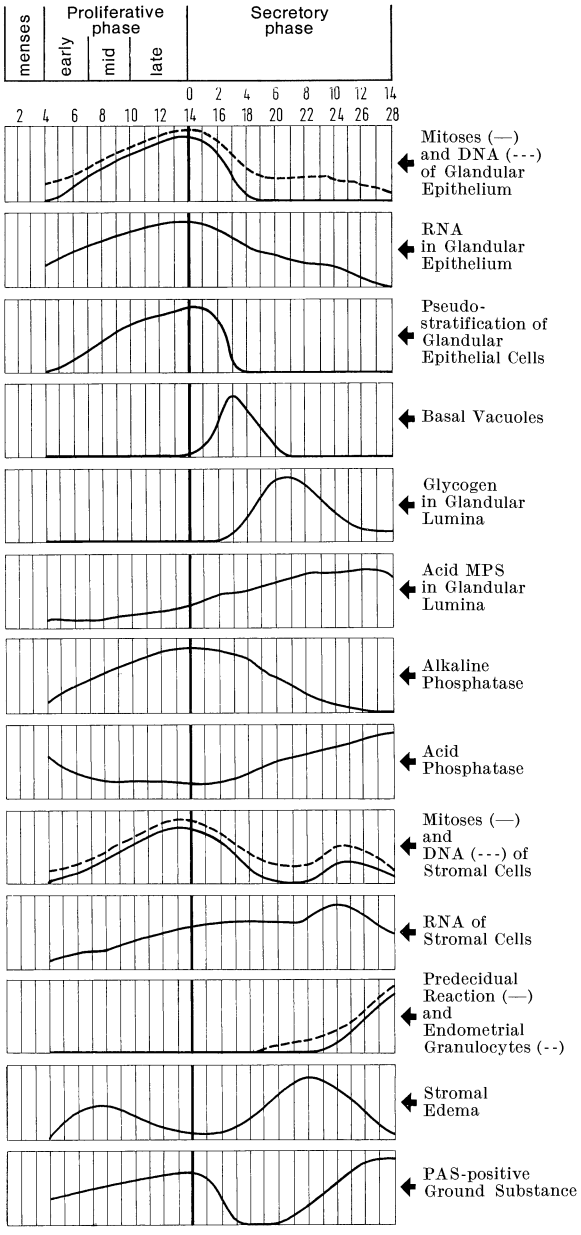


Fig. 11b. Morphologic criteria important in dating the endometrial cycle

normal and pathological conditions. Since hormones control the time and amount of DNA, RNA, glycogen, and mucus synthesized by endometrial cells, by determining these substances in histologic sections with special stains (particularly with acridine orange fluorochromation, the gallocyanin chromalum stain, and the PAS reaction) we can detect subtle changes in ovarian function (DALLENBACH and DALLENBACH-HELLWEG, 1968). By correlating that information with corresponding changes we see in hematoxylin-eosin stained sections prepared at the

same time, we learn how to accurately evaluate the routine "H. & E." sections and to determine what their limits of infallibility are. Such studies are indispensable for differentiating from the normal state the earliest variations produced by hormonal imbalance of endogenous or exogenous origin, and are of utmost importance for diagnosing functional changes. Although electron-microscopic studies may disclose finer details of hormonal action, they are of no help in recognizing functional disturbances. For that, a light microscope is needed, because the cyclic changes develop at somewhat different times from region to region or from cell to cell. To ascertain the extent of these differences, in order to date the endometrium accurately, we must examine all parts of the curettings carefully. Only the light microscope affords us such a thorough examination.

Although some investigators have elected to divide the menstrual cycle into three functional phases (FORBES and HEINZ, 1953; BARTELMEZ, 1957; STRAUSS, 1962; THEMANN and SCHÜNKE, 1963), I prefer to retain the customary division into the proliferative phase and the secretory phase. My reasons are: first, ovulation logically sets the two phases apart. Second, the differences in the amounts of the two ovarian hormones secreted during the cycle favors its division into two halves. Estrogen predominates in the proliferative phase, the progesterone effect prevails in the secretory phase. That the secretion of the hormones overlaps in both directions is well-known and to be expected in such a biological reaction.

a) The Normal Proliferative Phase

This phase generally lasts two weeks but under physiological conditions may fluctuate between ten and twenty days. Consequently, it is impossible to determine each day of the cycle during the proliferative phase. Therefore, we subdivide it only into the early, middle and late stages. The classification suffices since the important functional changes first become evident in the secretory phase. The proliferative phase is under the control of the growth stimulating hormone, estrogen. Only at the end of the phase do criteria appear, as revealed by special stains, that indicate ovulation is imminent. These criteria are of value in distinguishing a normal cycle from the anovulatory cycle.

The *early proliferative stage* (fourth to seventh day of a twenty-eight day cycle) is characterized by a low endometrium, and represents essentially a freshly epithelialized basalis. Its glands are sparse, narrow, and straight, embedded in a loose stroma of spindly cells. The regenerating superficial epithelium remains flat. The epithelial cells of the glands are low columnar; their cytoplasm contains little RNA. Their nuclei appear small, oval and the chromatin dense. Nucleoli are inapparent. The spindle-shaped stromal cells are all alike, poorly differentiated and well anchored in the reticulum network. The chromatin of their nuclei is dense, surrounded by scanty cytoplasm (Fig. 12).

As the effect of estrogen steadily intensifies, the endometrium gradually changes; a state is finally reached that we recognize as the *mid proliferative stage* (eighth to tenth day of a twenty-eight day cycle). The prime change characterizing this stage is the great increase in the height of the endometrium resulting from generalized stromal edema induced by estrogen. The glands not only keep

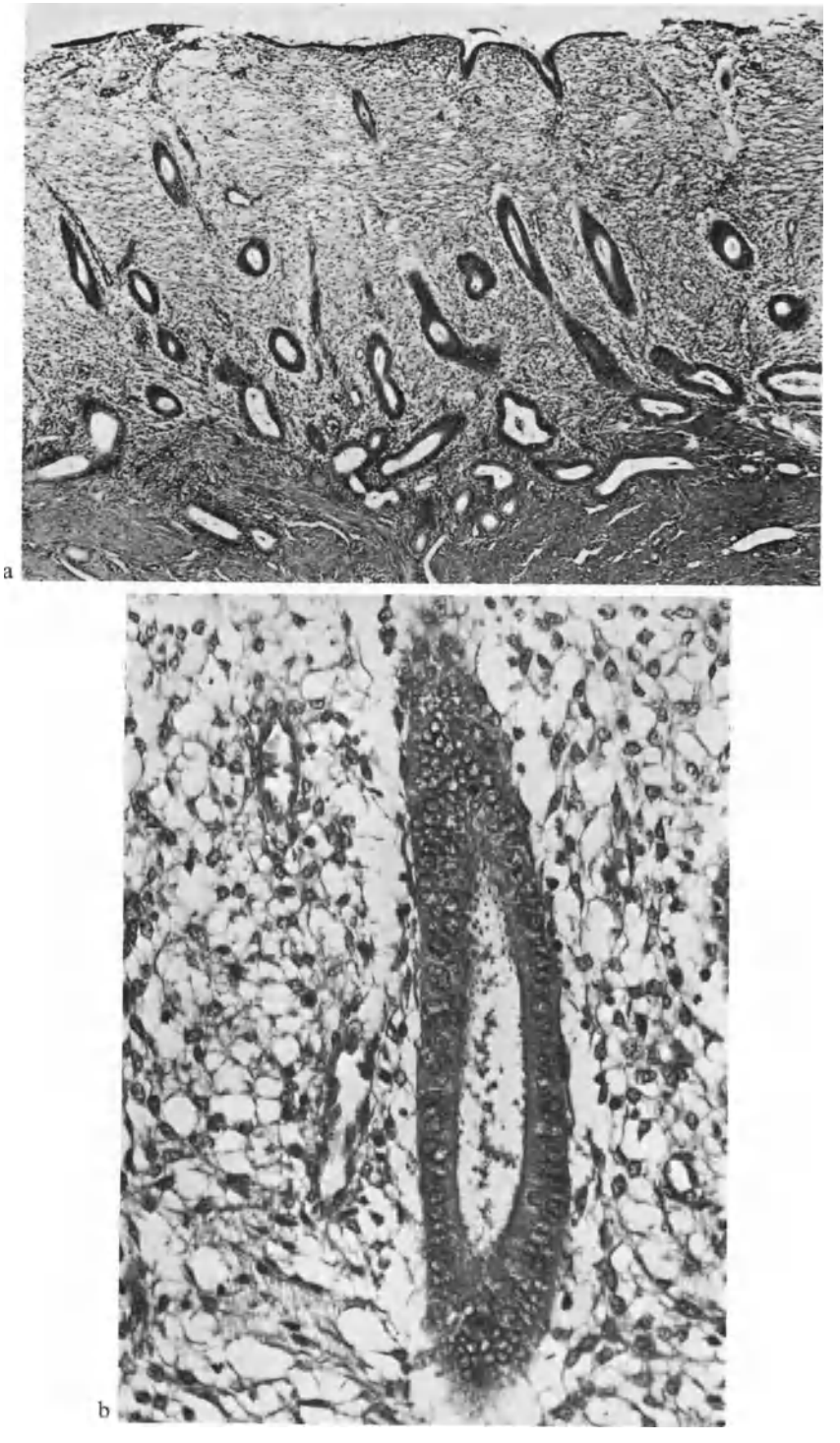


Fig. 12a and b. Early proliferative phase. Narrow, straight glands surrounded by a loose stroma of spindle-shaped cells. (a) Low magnification. (b) Higher magnification

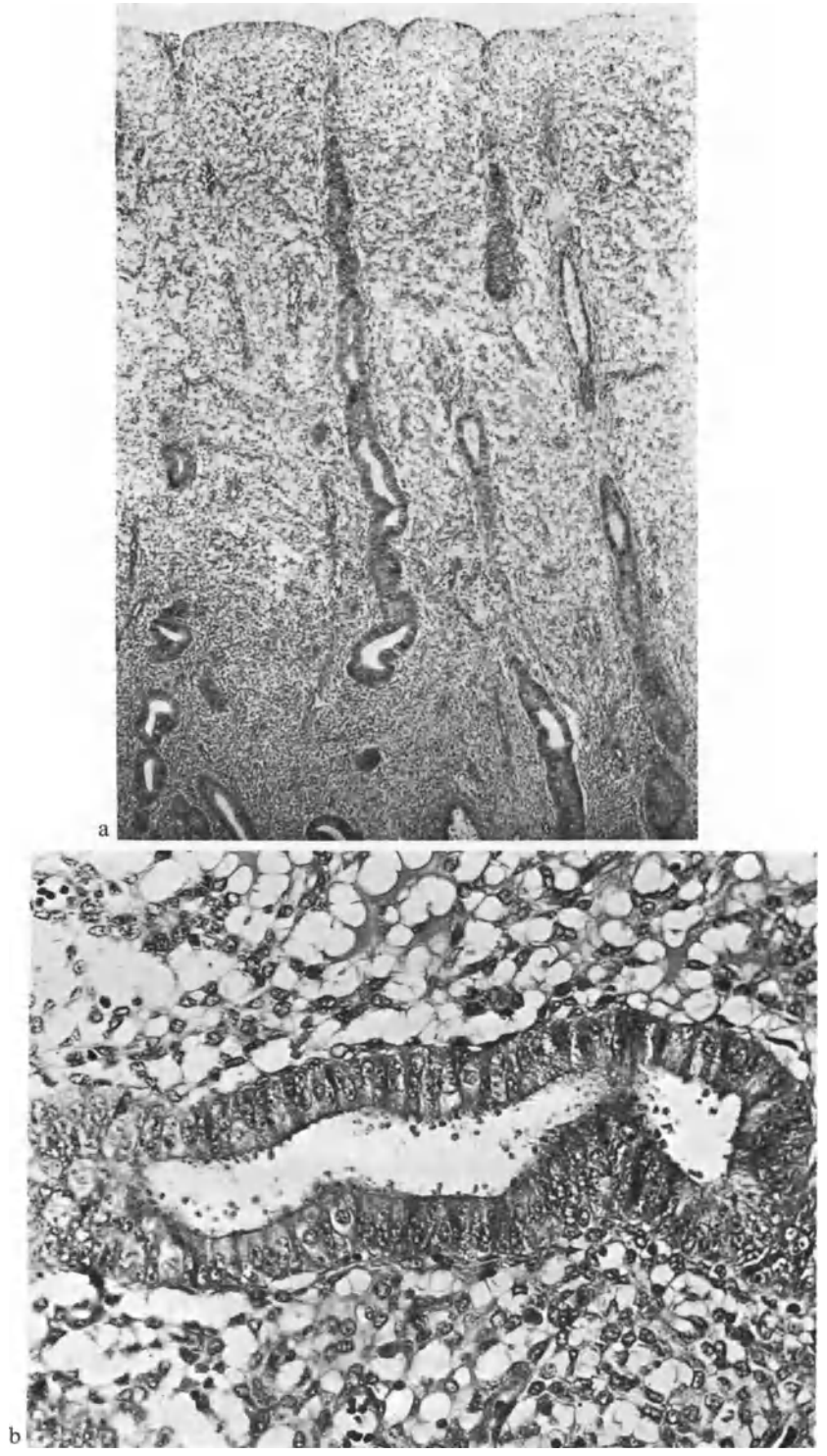


Fig. 13a and b. Mid-proliferative phase. Slight tortuosity of glands, stromal edema. (a) Low magnification. (b) Higher magnification

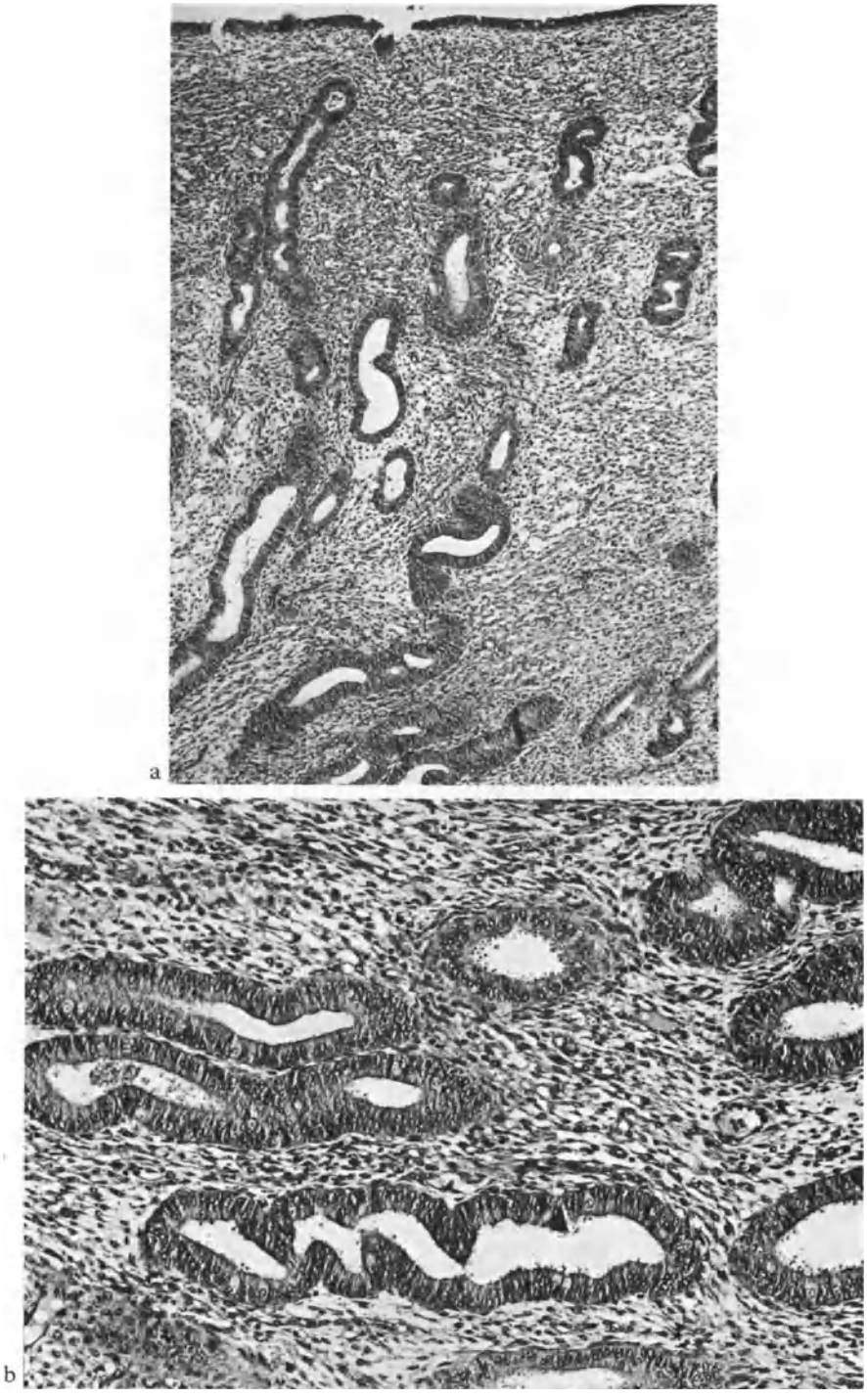
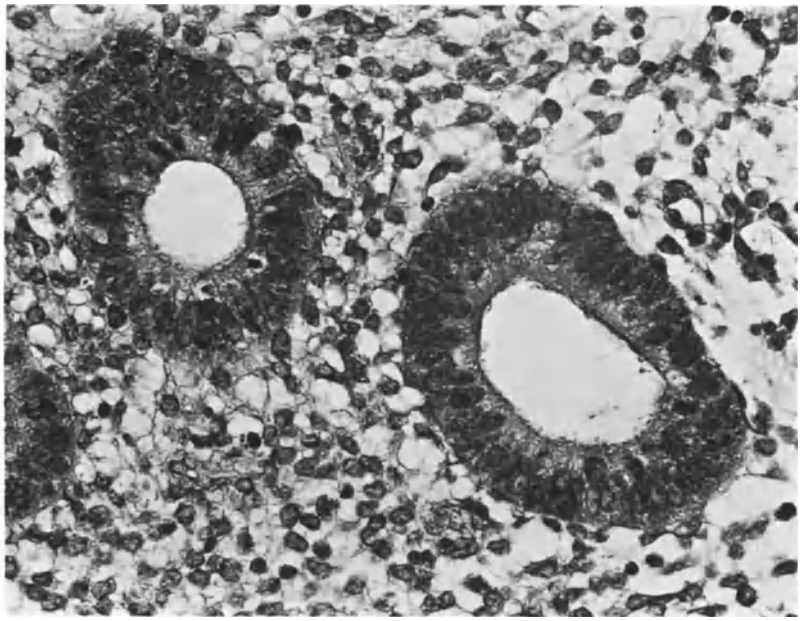


Fig. 14a–c. Late proliferative phase. Glands more tortuous, the epithelium pseudostratified, the stromal edema has subsided. (a) Low magnification. (b) Higher magnification

pace with that increase by rapidly growing longer but even exceed it, as their beginning tortuosity indicates. Their epithelial cells become compressed and tall columnar. Although the chromatin of their large, oval nuclei is still dense, nucleoli soon become apparent. In general, the nuclear content of DNA increases, as measurements have shown (HARKIN, 1956); many of the cells may be in mitosis. Usually, the cytoplasm of the epithelial cells now contains only a small amount of RNA. With appropriate histochemical methods we can demonstrate poorly polymerized acid mucopolysaccharides at the apical ends of the cells (STRAUSS, 1962). The epithelial cells of the endometrial surface also are of the tall columnar



c

Fig. 14c. High magnification

type. The spindle-shaped stromal cells, separated by the interstitial edema, lie attached to the reticulum network. Their cytoplasm is scanty; their fusiform nuclei are enlarged. Stromal cells in mitosis generally abound (Fig. 13).

The transition to the *late proliferative stage* (eleventh to fourteenth day of a twenty-eight day cycle) is marked by the regression of the edema. As that abates, the endometrium temporarily shrinks and as a result the glands, which continue to grow, become more tortuous. Although their epithelial cells continue to proliferate, increasing the tortuosity of the glands, the length to which they can grow is limited. Consequently, the epithelial cells lining them begin to pile up against one another with their nuclei at different levels, producing a pseudostratified appearance. Since all the cells maintain contact with the basement membrane, in some instances only by a thin cytoplasmic extension, the apparent multilayered epithelium is in fact just a single layer. The apical edges of the cells are now so sharp and smooth it appears as if the lumina of the glands had been punched out (Fig. 14). As the cytoplasm of the epithelial

cells increases and RNA accumulates, the nuclear-cytoplasmic ratio shifts gradually in favor of the cytoplasm. The nuclei, though enlarged, remain fusiform. They now contain several to many small nucleoli, which become especially prominent with acridine orange fluorochromation. Also at this time we will find tiny green granules of glycogen at the basal parts of the cells if we stain frozen sections with acridine orange and examine them under UV light. With the PAS reaction the granules are red (Color Plate I a). Their appearance before ovulation indicates that the ovary has already begun to secrete progesterone. Minute amounts of progesterone have been detected in the blood of patients at this time (HOFFMANN, 1948; EDGAR, 1952; FORBES, 1953; ZANDER, 1954). From the results of studies in animals it seems most likely that the progesterone is secreted by the theca interna of the mature Graafian follicle (MCKAY and ROBINSON, 1947). The lumina of the glands are either empty or contain at most scanty, ill-defined substance composed in part of proteins and mucopolysaccharides shed by the cells (STRAUSS, 1962; SCHMIDT-MATTHIESEN, 1963). The stromal cells, again compact because the edema has subsided, have in the meantime enlarged and proliferated; their nuclei bear prominent nucleoli. The stromal cells in the upper half of the functionalis have especially abundant RNA in their enlarged cytoplasm, whereas the stromal cells of the lower half contain only sparse amounts. We can clearly distinguish these two layers, which correspond later to the compacta and spongiosa, with acridine orange fluorochromation since the more the RNA, the redder the cells fluorescence. With hematoxylin-eosin stained sections, however, RNA fails to stain specifically, thus the differences in the two layers go undetected.

The estrogen effect, optimal when it lasts two weeks, leads to the buildup of the functionalis through growth and proliferation of the glands and stromal cells. With their high content of RNA, the cells of the superficial stroma and glands are ideally primed by the time ovulation occurs and are receptive to progesterone and the differentiation it induces.

b) The Normal Secretory Phase

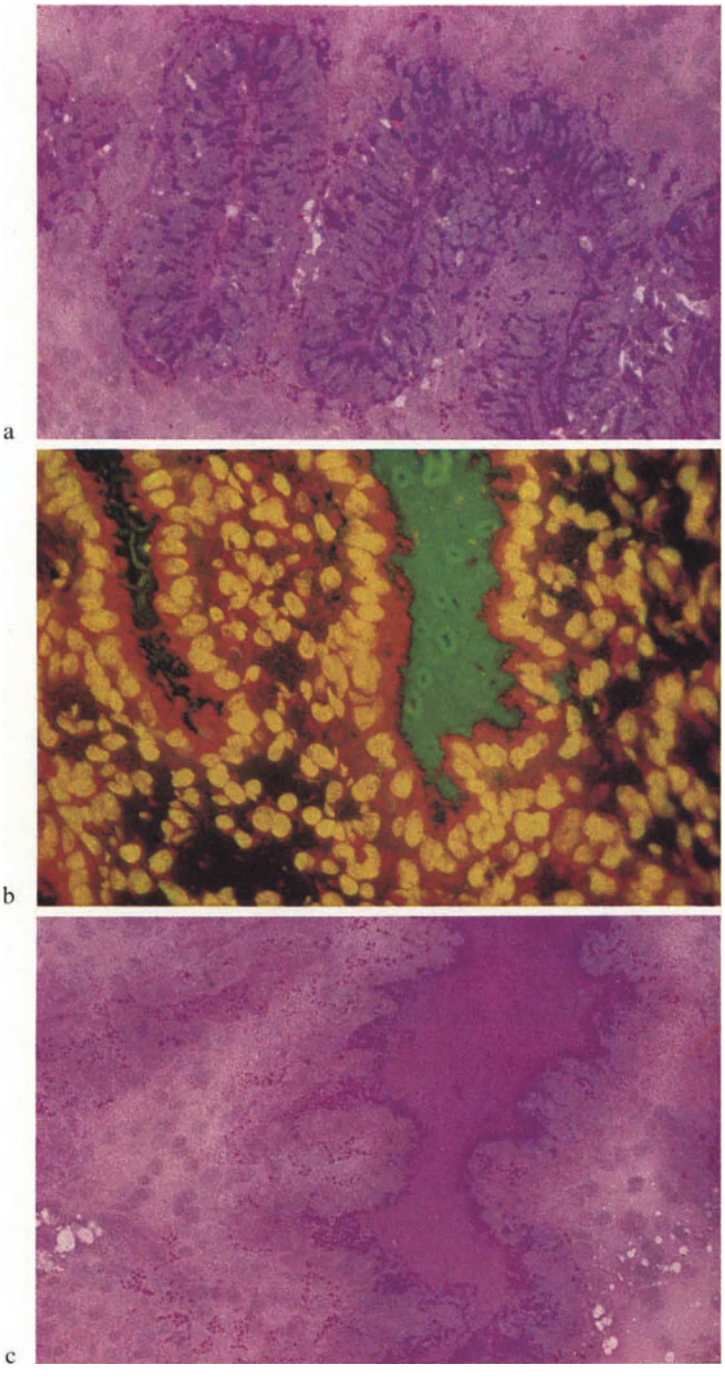
After ovulation the normal corpus luteum develops and involutes at a definite rhythm in a precise sequence, causing changes in the endometrium to take place at the same rate. Consequently, the normal secretory phase of most cycles lasts fourteen days (± 1) (ROCK and HERTIG, 1944; ZUCKERMAN, 1949). If that limit is decreased (or exceeded) by more than two days, then we should diagnose

Color Plate I

(a) Endometrium at the end of the proliferative phase. Beginning secretion of glycogen as droplets in the basal cytoplasm of the glandular epithelium. Unfixed cryostat section. Stain: PAS

(b) Seven days after ovulation. The dilated glandular lumen is filled with green staining glycogen, the apical ends of the glandular cells are frayed. Unfixed cryostat section. Acridine orange fluorochromation

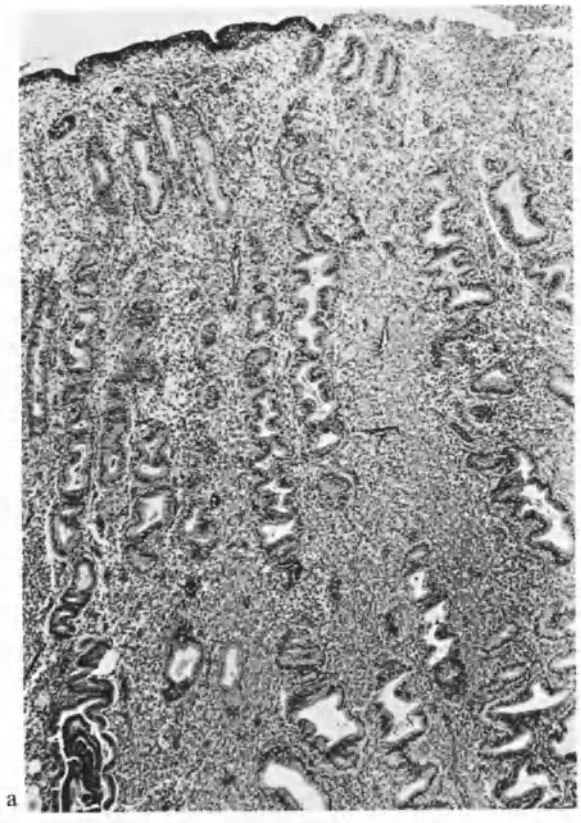
(c) Same endometrium as in (b). The glycogen in the lumen red. Unfixed cryostat section. Stain: PAS



Color Plate I

a pathological shortening (or lengthening) of the secretory phase. In order to evaluate such fluctuations precisely, the clinician must determine the time of ovulation just as accurately as we define the morphological changes and criteria that occur in the endometrium. The peak of LH signalizes ovulation more precisely than does the measurement of the basal temperature (KONINCKX *et al.*, 1977). The greater fluctuations in the length of the secretory phase occasionally observed (variations between nine and sixteen days) most probably cause the sterile cycles that occur sporadically in healthy, sexually mature women. Such deviations are most frequent at the beginning and end of the childbearing period (SCHRÖDER, 1913, 1928; VOLLMAN, 1967; TRELOAR *et al.*, 1967). Since the corpus luteum develops and involutes at a definite rate and rhythm, the associated changes regularly induced in the endomentrium enable us to date the endometrium (to diagnose the day of the cycle). Histological changes in the endometrium serve as our criteria. Whereas the changes in the glandular epithelium during the first week of the secretory phase are more striking and easier to detect, during the second week we base our histological dating chiefly on the daily changes that take place in the stromal cells. The histological and cytological changes induced in the endometrium by the sex hormones are never uniform. Some cells in some regions always reveal greater differentiation than cells in other parts although adjacent. Such differences are related to many variable factors, such as differences in local blood supply, in amounts of hormones reaching the target cells, and in cellular nutrition and metabolism. We should therefore never expect the endometrium to present the same picture in all equivalent parts. In dating the endometrium we should be guided by those regions showing the most advanced changes or by the appearance of the majority of the cells.

The *first day after ovulation* (fifteenth day of an ideal cycle) is morphologically "mute" because it takes thirty-six to forty-eight hours before the initial progesterone secreted by the corpus luteum produces enough change to be detected in hematoxylin-eosin stained sections. Since sporadic vacuoles appear in some of the glandular epithelial cells in the first hours after ovulation and since deposits of glycogen, as revealed by special stains, may occasionally form just before ovulation, these vacuoles and deposits are unreliable as definite signs that ovulation has taken place. The earliest that ovulation can be detected with certainty is 36 hours later; that is, on the *second day* (sixteenth day of the cycle) when numerous basal vacuoles appear in the glandular epithelium. The endometrium should not be dated as the sixteenth day, however, unless at least 50 per cent of the glands have basal vacuoles. In hematoxylin-eosin sections the vacuoles are produced by the dissolving away of glycogen that formed basally and pushed the nucleus towards the lumen. By this second day the epithelial cells again form a single row. The glands continue to grow longer and become increasingly more corkscrew-shaped (Fig. 15). As a consequence, the entire surface of the epithelium greatly increases, a change that promotes the secretion soon to occur from that surface into the glandular lumen. At this time fairly brisk hemorrhages may develop in the stroma ("physiological ovulatory bleeding" (Fig. 16), if the transient fall of estrogen at ovulation is great or if the capillaries prove to be unusually sensitive to that decrease in estrogen.



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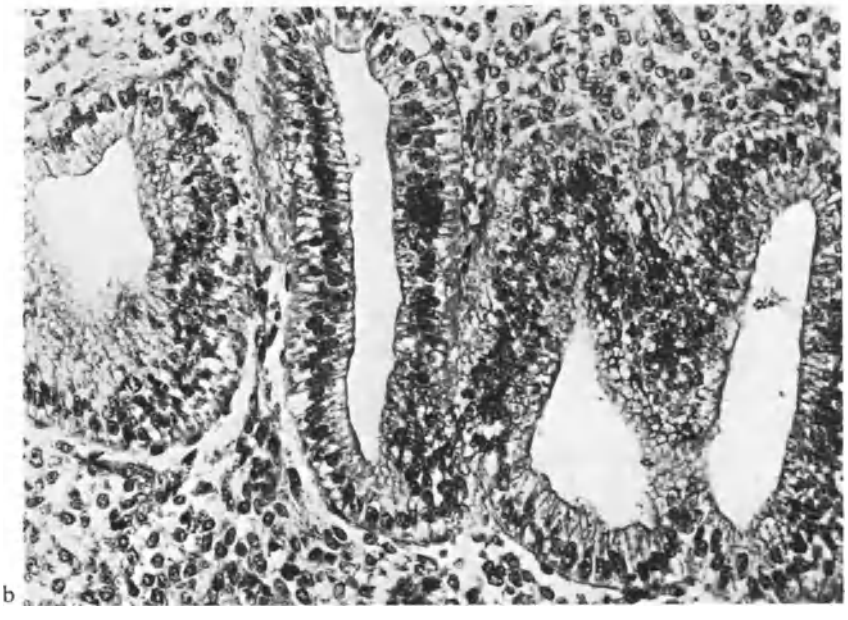


b

Fig. 15a and b. The second day after ovulation. Prominent tortuosity of glands; basal vacuoles begin to appear in the glandular epithelial cells. (a) Low magnification. (b) Higher magnification

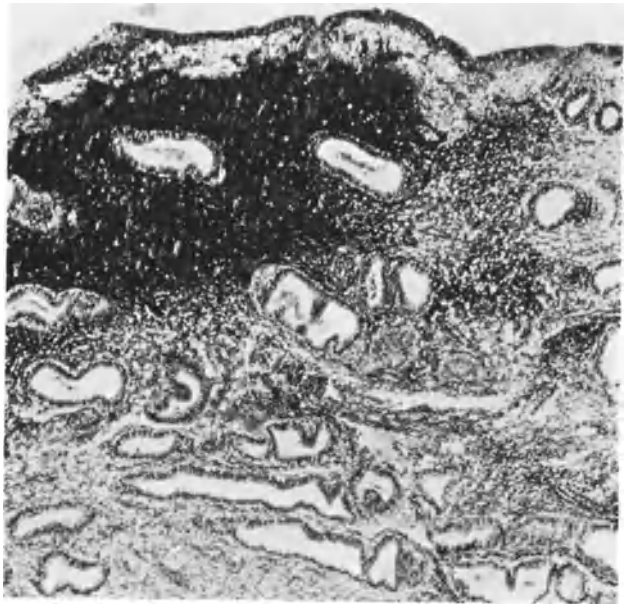


Fig. 16. Ovulatory bleeding: Focal extravasation of blood in the superficial stroma

Whereas most of the glandular epithelial cells on the second day after ovulation disclose basal vacuoles, by the *third day* these vacuoles have enlarged to push all nuclei toward the apical end of the cell where they form a uniform row around the lumen (Fig. 17). Few mitoses are to be found since the epithelial cells generally lose their ability to divide with the onset of this specific differentiation brought on by progesterone. The nuclear-cytoplasm ratio now is clearly in favor of the cytoplasm (1:3.6) (STURGIS and MEIGS, 1936). The cytoplasm still contains abundant RNA. As histochemical studies disclose, acid mucopolysaccharides begin to accumulate at the apical rim of the cell.

On the *fourth day* after ovulation some of the nuclei return to the base of the cell (Fig. 18), while the glycogen on both sides of the nucleus moves towards the lumen, a shift that is particularly easy to follow with the PAS reaction.

On the *fifth day* after ovulation most of the nuclei have returned to the base of the cell. The accumulated glycogen located now above the nucleus is secreted at the free margin as a globular cap, which bulges into the lumen (Fig. 19). The cytoplasm is still rich in RNA. The nuclei are round, vesicular and unusually clear or pale staining, making it easy to distinguish them from the dense, elongated nuclei that were basal just before the glycogen vacuoles appeared. The nucleoli by now have greatly enlarged.

The *sixth day* after ovulation is characterized by a dilatation of the glandular lumina produced by the continued secretion of glycogen (Fig. 20). The apical ends of the low glandular cells appear shredded with hazy margins owing to the apocrine secretion. Since the RNA content of the cytoplasm gradually falls

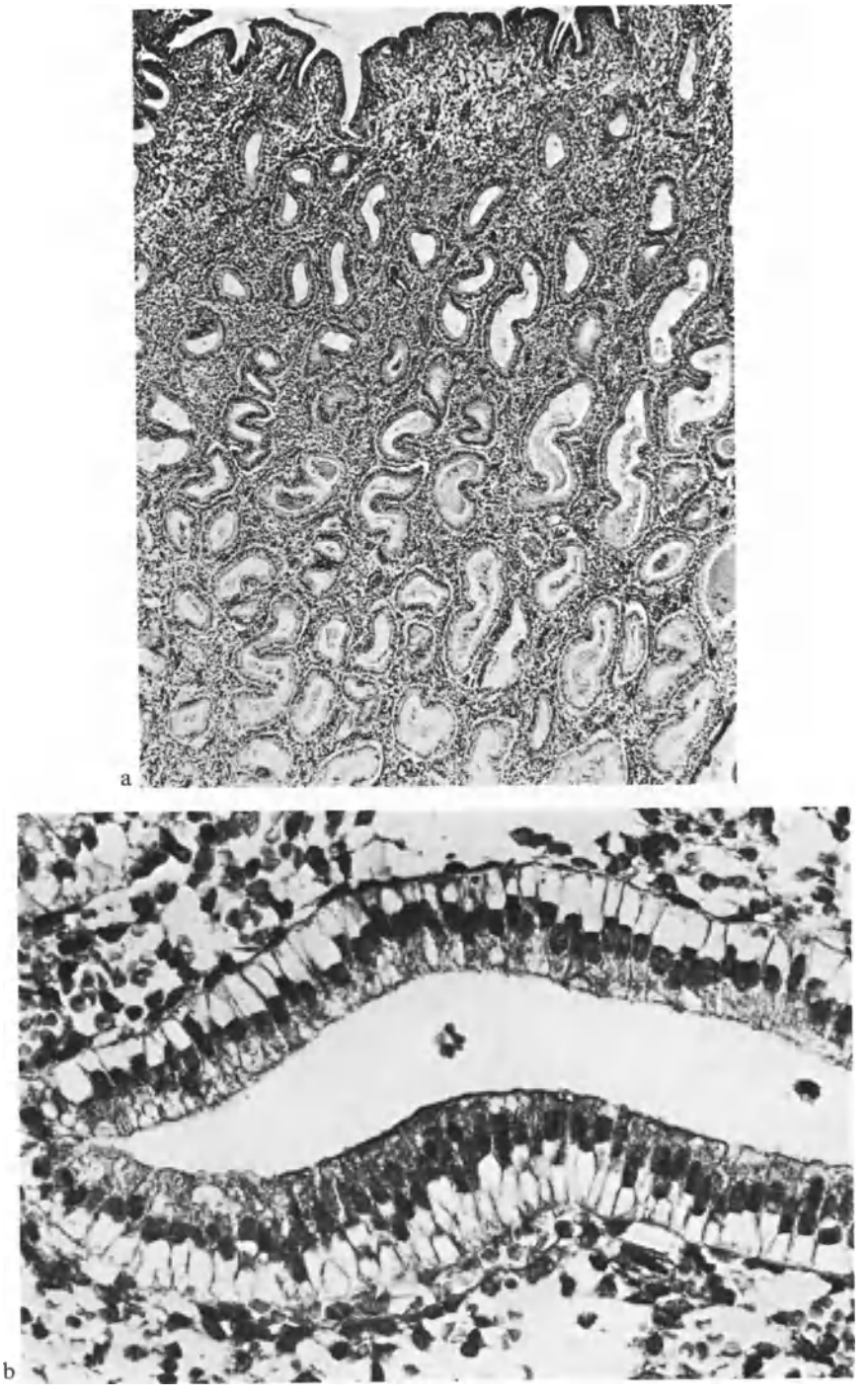


Fig. 17a and b. The third day after ovulation. Distinct basal vacuoles in all glandular epithelial cells. The nuclei generally still elongated. (a) Low magnification. (b) Higher magnification

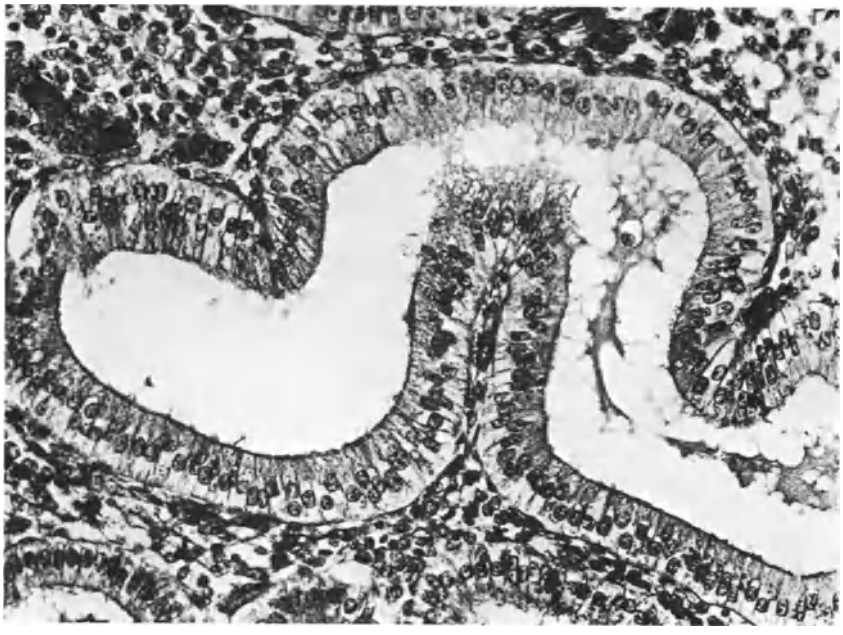


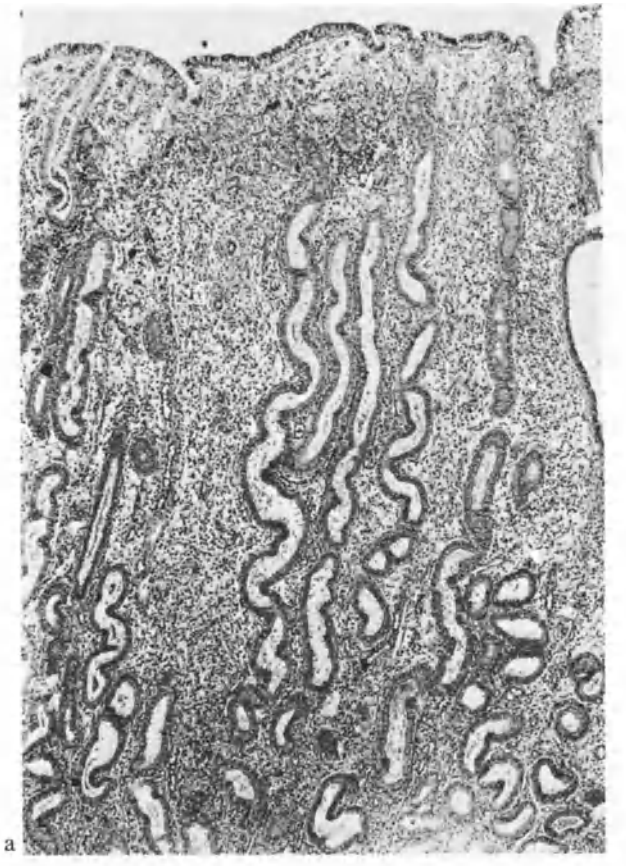
Fig. 18. The fourth day after ovulation. Basal vacuoles still readily visible. The nuclei more rounded

but the nucleoli remain large, it seems probable that the nuclear RNA ceases to be discharged into the cytoplasm.

In the ensuing days of the cycle, which are diagnosed primarily from the changes taking place in the stroma, the secretion distending the glandular lumina becomes thicker (Color Plate I b and c), becomes intermixed with acid and neutral mucopolysaccharides, and through polymerization becomes stringy and metachromatic; gradually it disappears. Although we find glycogen in the glandular lumen only until the seventh day after ovulation, remnants of acid and especially neutral polysaccharides remain at the apical end of the cell and in the glandular lumen until shorty before menstruation. The glandular cells become more cuboidal and their stores of RNA continue to decrease; a few days before menstruation starts their RNA is depleted.

During the first week of the secretory phase little happens to the endometrial stroma, as compared with the drastic changes that take place in the glandular epithelium. During the second week, however, changes in the stroma make it possible to readily subdivide the functionalis into the compacta and the spongiosa. On the *seventh day* after ovulation stromal edema develops again (Fig. 21), reaching its maximum on the *eighth day* (Fig. 22) when the secretion of estrogen

Fig. 19a and b. The fifth day after ovulation. The basal vacuoles are fading away and the nuclei are returning to the base of the cell; beginning secretion of glycogen. Slight stromal edema. (a) Low magnification. (b) Higher magnification



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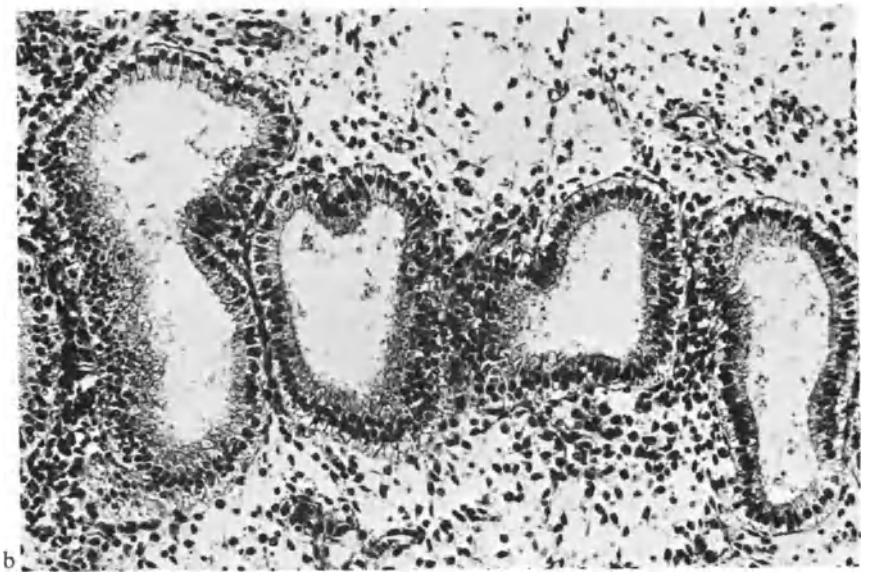

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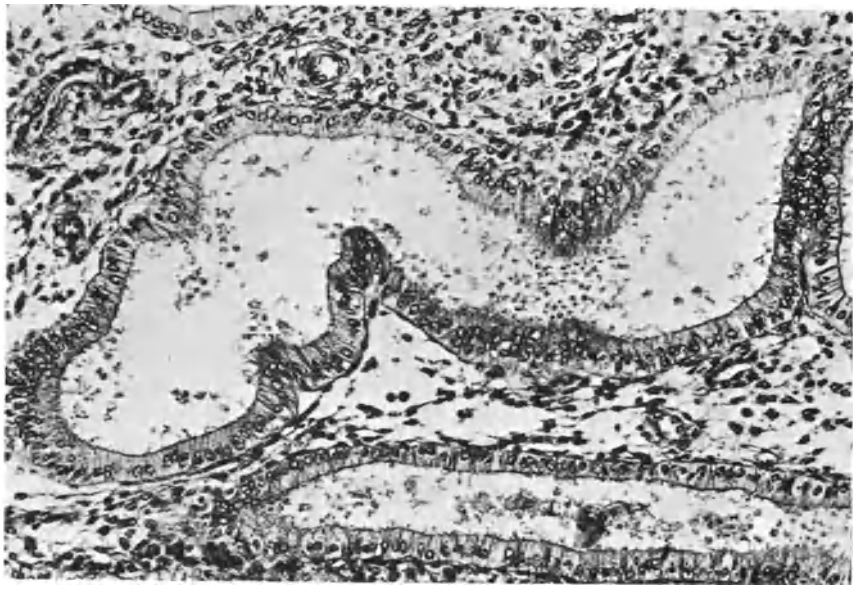


Fig. 20. The sixth day after ovulation. The nuclei are now almost entirely basal. The glandular lumen begins to dilate with fine droplets of glycogen

during the secretory phase is also at its highest. Although the stromal cells are now somewhat larger, they are still spindle-shaped; the edema fluid causes them to become widely separated. Mitoses cease to appear.

As the edema subsides on the *ninth day* after ovulation, groups of spiral arterioles become prominent (Fig. 23). During the proliferative phase these vessels have a straight course, but in the secretory phase, owing to the effects of progesterone, they grow much longer, thicker, and become spirally twisted. Although the volume of the endometrium doubles in the secretory phase, the volume of the arterioles enlarges threefold (MASSHOFF and KRAUS, 1955) and their length increases fivefold (MARKEE, 1950). It is obvious that the growth of these vessels exceeds that needed for mere nutrition of the endometrium. The stromal cells surrounding these spiral arterioles grow larger, become rounded and their content of RNA markedly increases.

On the *tenth day* these periarteriolar stromal cells turn into predecidual cells, forming prominent, broad mantles about the vessels. The nuclei of the cells are large, round, and clear (Fig. 24; Color Plate IIa). Among the predecidual cells, and almost as numerous as they, are small endometrial granulocytes with lobated, chromatin-rich nuclei and characteristic phloxinophilic granules in their cytoplasm, which also contains abundant RNA (HAMPERL, 1954; HELLWEG, 1954). Thus, as one might expect, the first stromal cells to undergo differentiation by rounding up to become predecidual cells or by freeing themselves from the reticulum network to turn into small granulocytes are those nearest the arterial blood supply; that is, those first to be affected by progesterone.

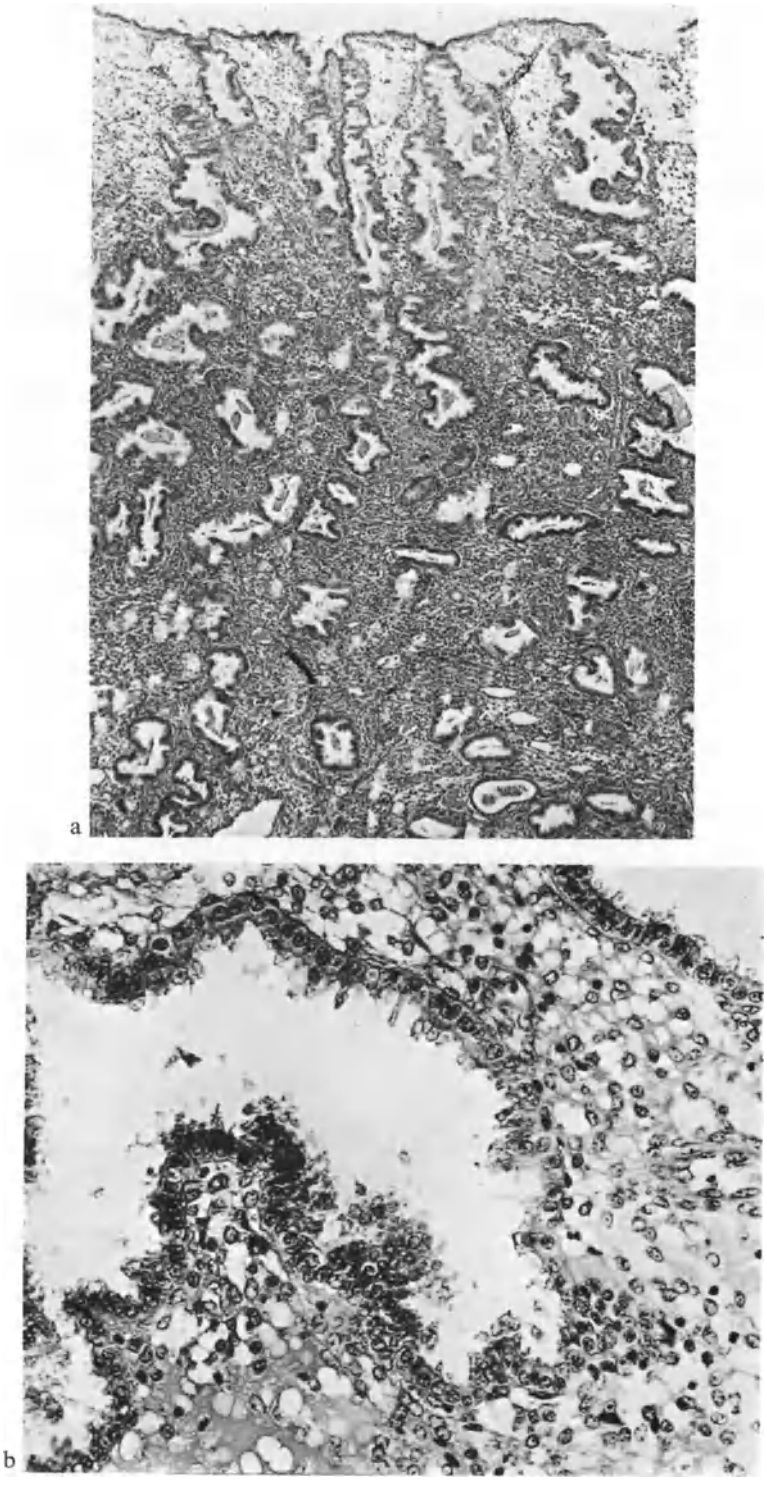
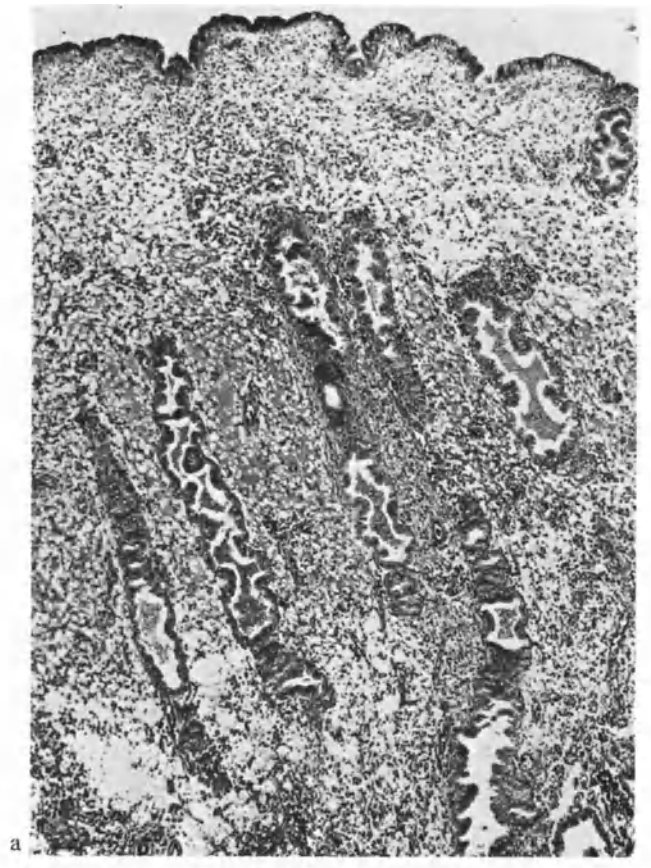


Fig. 21 a and b. The seventh day after ovulation. The glandular lumen dilated with abundant glycogen. The border of glandular epithelium appears shredded owing to intense secretion. (a) Low magnification. (b) Higher magnification



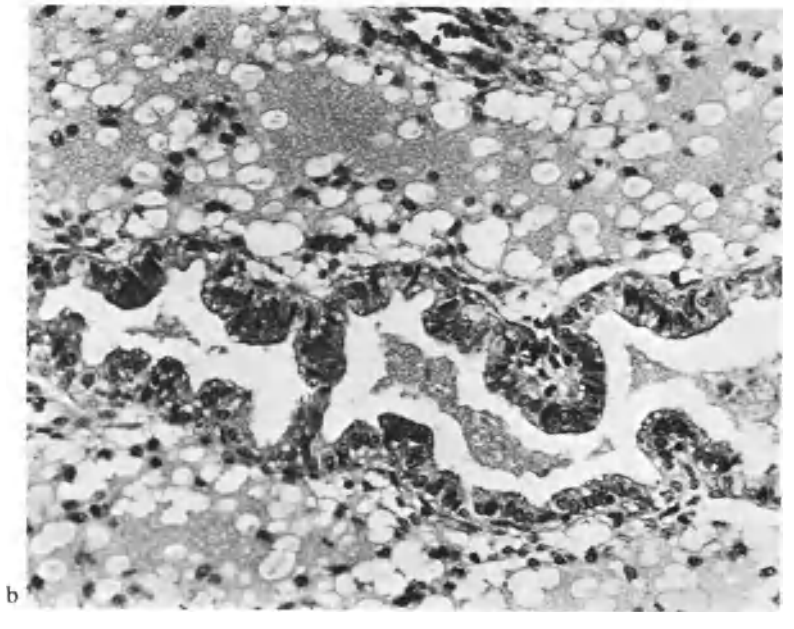


Fig. 22a and b. The eighth day after ovulation. Glandular lumina still contain traces of glycogen, intermixed with mucopolysaccharides. Greatest stromal edema during secretory phase. (a) Low magnification. (b) Higher magnification

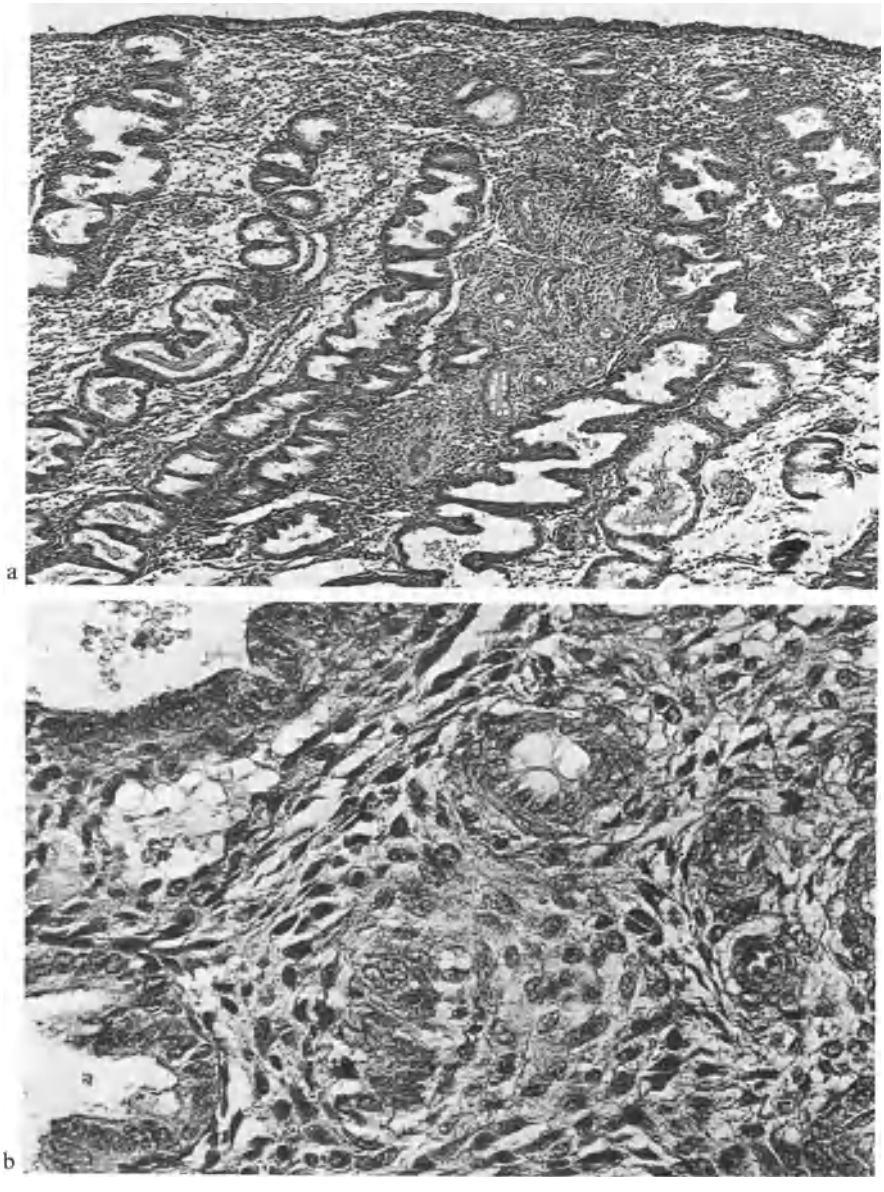


Fig. 23a and b. The ninth day after ovulation. Stromal edema and glycogen secretion abate, first evidence of predecidual reaction around spiral arterioles. (a) Low magnification. (b) Higher magnification

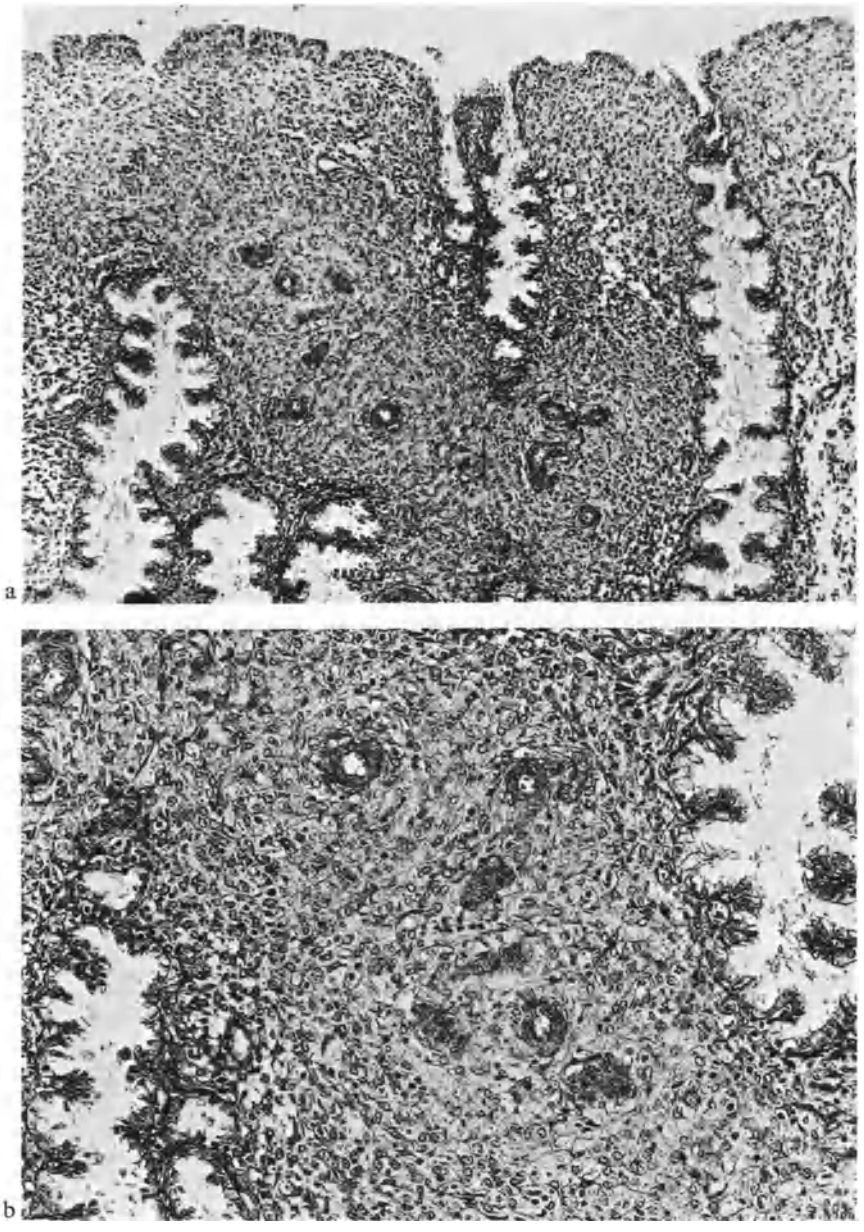


Fig. 24a–c. The tenth day after ovulation. Almost sheetlike predecidual reaction around the spiral arterioles and beneath the superficial epithelium. (a) Low magnification. (b) Higher magnification. (c) The glandular epithelium in the spongiosa is prominently dentated. Residual secretion in the glandular lumen

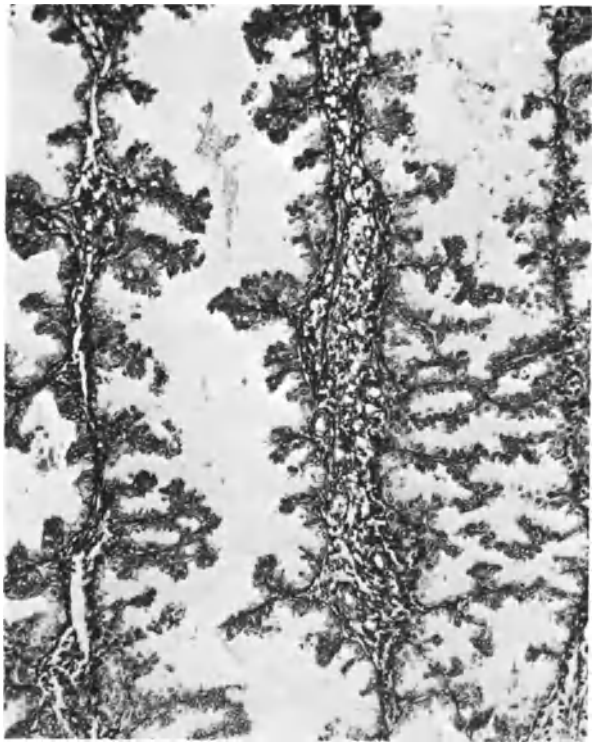


Fig. 24c. Legend see opposite page

By the *eleventh day* after ovulation the stromal cells of the upper compacta located close to the superficial epithelium differentiate into predecidual cells and granulocytes (Fig. 25); by the *twelfth day* the entire compacta discloses that transformation. Numerous lacunae of dilated capillaries appear close to the surface. When the corpus luteum begins to regress (four days before menstruation sets in, since pregnancy has failed to take place), we begin to see the first signs of endometrial involution with incipient shrinkage (Fig. 26).

On the *thirteenth day* after ovulation the endometrium greatly contracts because of the fall in both progesterone and estrogen. The glands collapse, assuming a saw-toothed appearance (Fig. 27), and the predecidual stroma becomes very dense.

On the *fourteenth day* the Golgi apparatus of the stromal and glandular cells involutes and the remaining RNA in these cells disappears. As the reticulum network disintegrates the stromal cells dissociate (Fig. 28). Occasionally one can find nuclear debris in the glandular cells, corresponding no doubt to the hematoxylin positive granules described by SCHRÖDER (1914). By now the endometrial granulocytes have given off their phloxinophilic granules and can at times be recognized only by their characteristic lobated nuclei and their vacuolated cytoplasm.

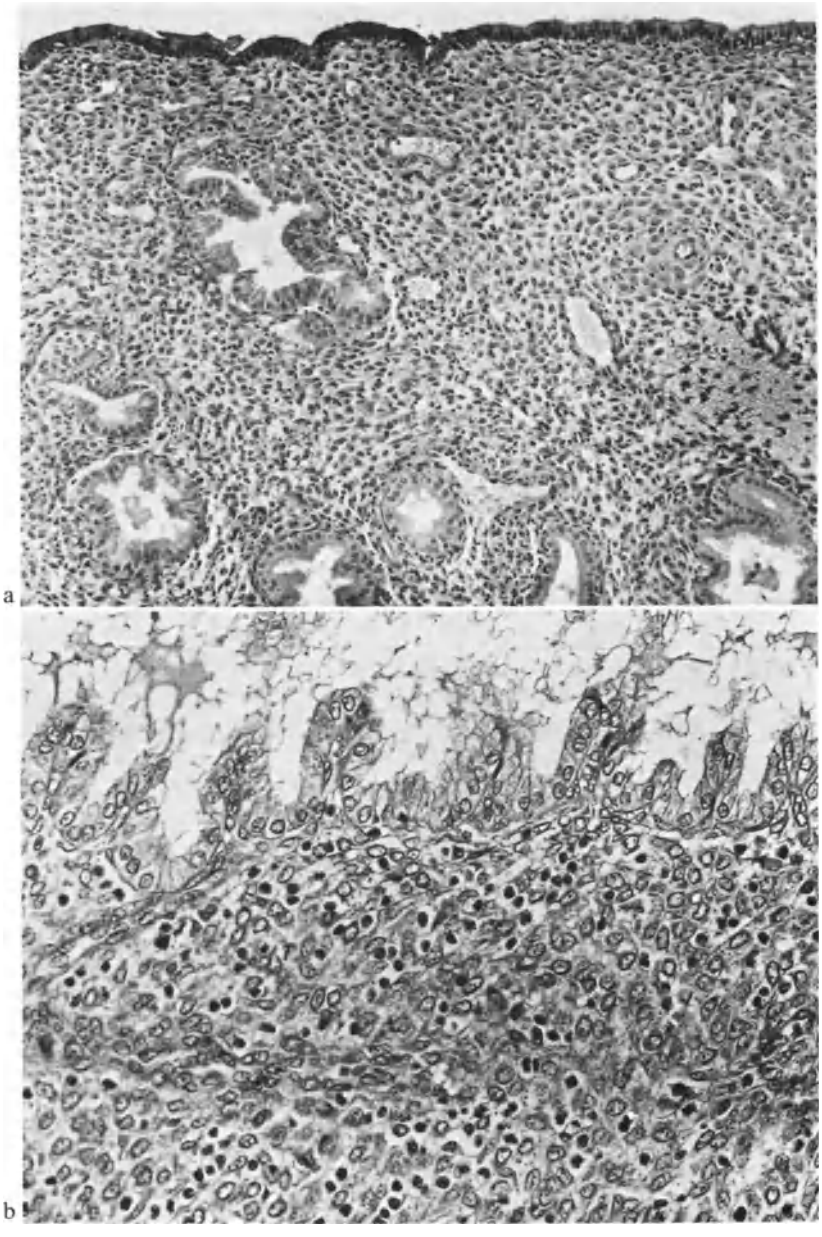


Fig. 25a and b. The eleventh day after ovulation. Predecidual transformation of the entire compacta, numerous endometrial granulocytes. (a) Low magnification. (b) Higher magnification

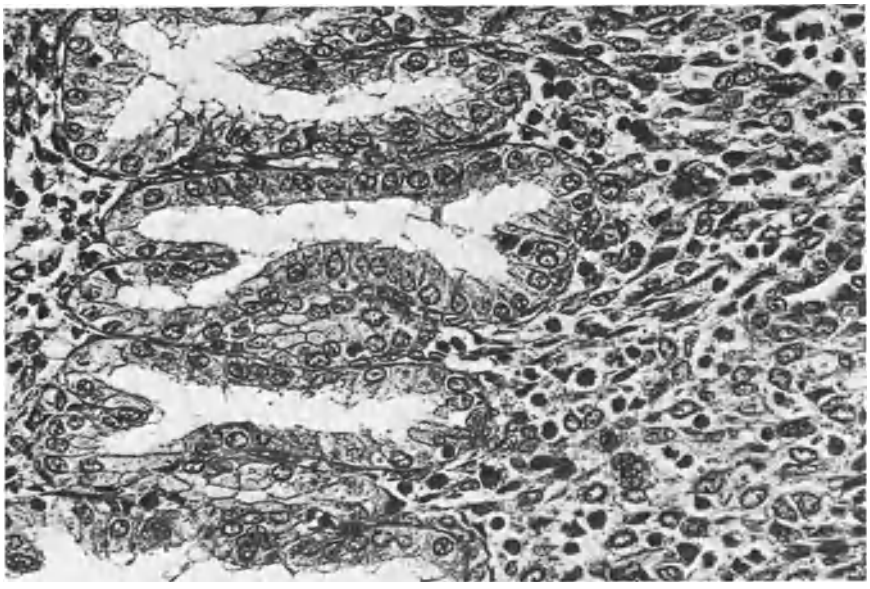


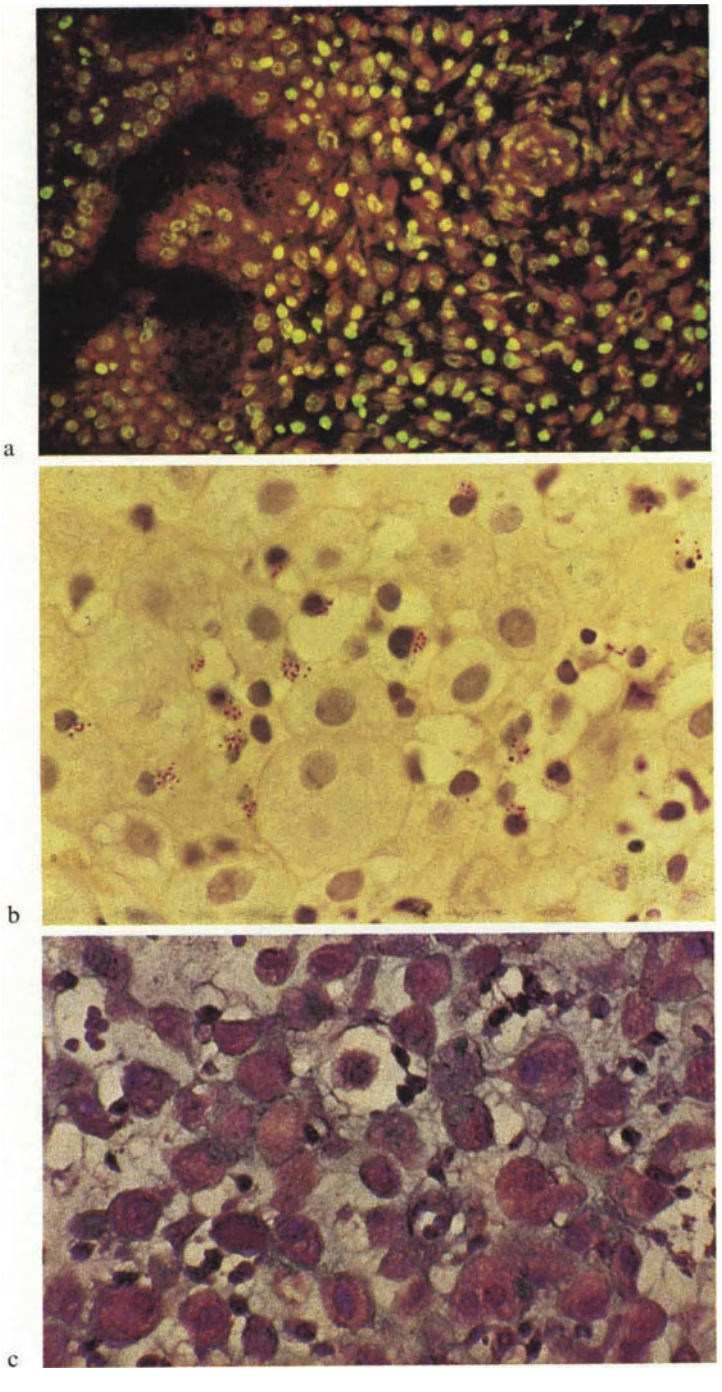
Fig. 26. The twelvth day after ovulation. The glands are beginning to collapse

c) Menstruation

The *first day* of menstruation is characterized by hemorrhage in the superficial stroma, whose dissociated cells still show their predecidual change (Fig. 29). From the remaining evidences of that change and from the occasional persisting signs of previous secretion in the epithelium of the collapsed glands, it is possible after the onset of menstruation to still diagnose that ovulation had taken place.

On the *second day* of menstruation one normally finds only scattered stromal cells and remnants of glandular epithelium liberated from their cellular connections, lying amid fresh blood and aggregates of polymorphonuclear leukocytes (Fig. 30). Contrary to earlier opinions, polymorphonuclear leukocytes are not found in a healthy endometrium before menstruation starts. The investigators who thought so mistook endometrial granulocytes for leukocytes.

The much-discussed question about the *cause of menstruation* remains incompletely understood even today, as the many theories that have been proposed for it testify; they all lack sufficient experimental confirmation. The most fundamental experiments carried out until now were made in monkeys. From the results we may assume the following is probably true: with the premenstrual fall of both hormones, especially estrogen, the endometrium loses water and greatly shrinks. According to some authors (MARKEE, 1940, 1950; WITT, 1963) the shrinkage is 20 per cent of the original height, but BARTELMEZ (1931, 1941, 1957) estimates it to be as much as 40 per cent. Such a 40 per cent shrinkage has been observed to occur in an endometriosis of the vagina (HOFFMANN *et al.*, 1953). In rare instances nothing more takes place at menstruation than the loss of water and the shrinkage of the endometrium; a real menstrual flow



Color Plate II

may fail to develop (BENGTSSON and INGEMANNSSON, 1959; PHILIPPE *et al.*, 1966). As the shrinkage progresses the spiral arterioles (DARON, 1936) and veins (DARON, 1937) collapse and kink, leading to ischemia and impairment of cellular respiration (BURGER, 1958). With the collapse of the arterioles, further factors act to aggravate the ischemia, such as a contraction of the smooth muscle cells of the media (BARTELMEZ) and a development in the arterioles of hyaline degeneration with loss of elastic fibers (KELLER, 1911). The capillaries also become more fragile. In addition, the fall in the progesterone activates fibrinolytic enzymes and induces the release of relaxin from the endometrial granulocytes, which in turn brings about dissolution of the stromal fibers (DALLENBACH and DALLENBACH-HELLWEG, 1964). That dissolution must take place before the stromal cells can dissociate and the functionalis can break down to be discharged as menstruating endometrium. Some authors maintain that a part of the spongiosa normally remains and partakes in the regeneration of the next cycle (SEKIGA, 1924; BARTELMEZ, 1933, 1941; ROCKENSCHAUB, 1960; MCLENNAN and RYDELL, 1965; SENGEL and STOEBNER, 1970). Contrarily, BOHNEN (1927) always observed a complete shedding of the spongiosa followed by epithelialization of the basalis. Most probably the extent to which the endometrium is desquamated depends on individual variations.

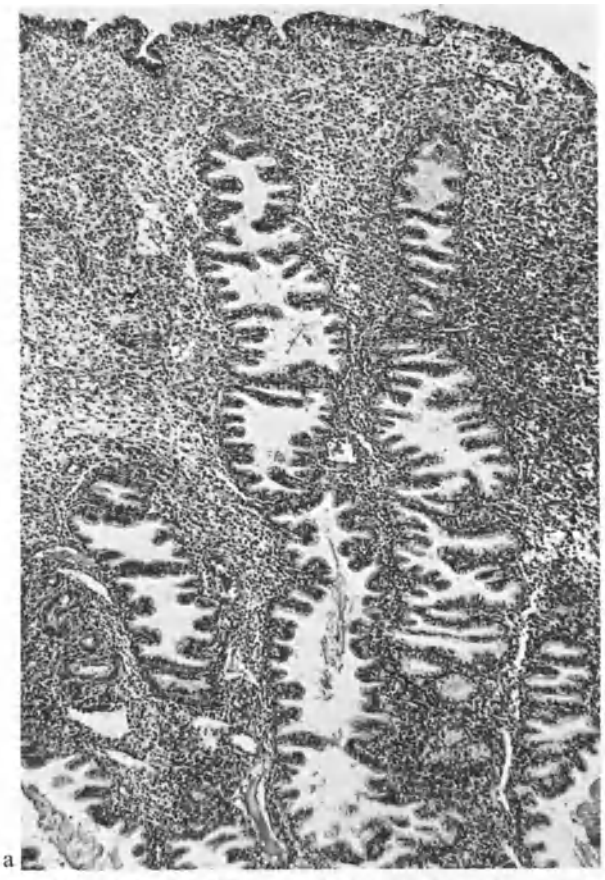
In general, the endometrium is discharged at those levels where it contains enough granulocytes to induce dissolution of the reticulum fibers. Normally, these cells pervade the compacta and part of the spongiosa, becoming increasingly sparse towards the basalis. During menstruation regressive changes begin in the parts of the endometrium not shed that enable the glandular and stromal cells here to survive, restore themselves, in order to participate in the physiological buildup of the next cycle. When bleeding commences, the epithelial and stromal cells engage in processes of "cellular and tissue self-cleaning and rejuvenation". These processes can best be followed with histochemical and electron microscopic methods and are seen as: autophagocytosis regulated by the cell's own lysosomes, heterophagocytosis performed by wandering macrophages, and discharge of cellular debris (FLOWERS and WILBORN, 1978) through intercellular spaces (DAVIE *et al.*, 1977) or through epithelial cells for elimination into glandular lumina and the uterine cavity. The remaining cells rejuvenate. Consequently, menstruation represents two main processes: first, the loss of tissue, the amount of which varies from patient to patient; second, a complicated interplay of cellular regression, restoration and renewal in the parts of the

Color Plate II

(a) The tenth day after ovulation. Stromal cells show predecidual change, especially about the spiral arterioles (in upper right), and abundant intracytoplasmic RNA (fluorescing red). The condensed nuclei of endometrial granulocytes stain intensely for DNA (fluorescing bright yellow). Unfixed cryostat section. Acridine orange fluorochromation

(b) Young decidua of second month of pregnancy. Numerous small endometrial granulocytes with paranuclear phloxinophilic granules between large decidual cells. Paraffin section. Stain: Phloxine-tartrazine

(c) Involuting decidua after abortion in third month. Blue-staining "collagen inclusions" in the shrinking and dissociating cells. Paraffin section. Trichrome stain after MASSON



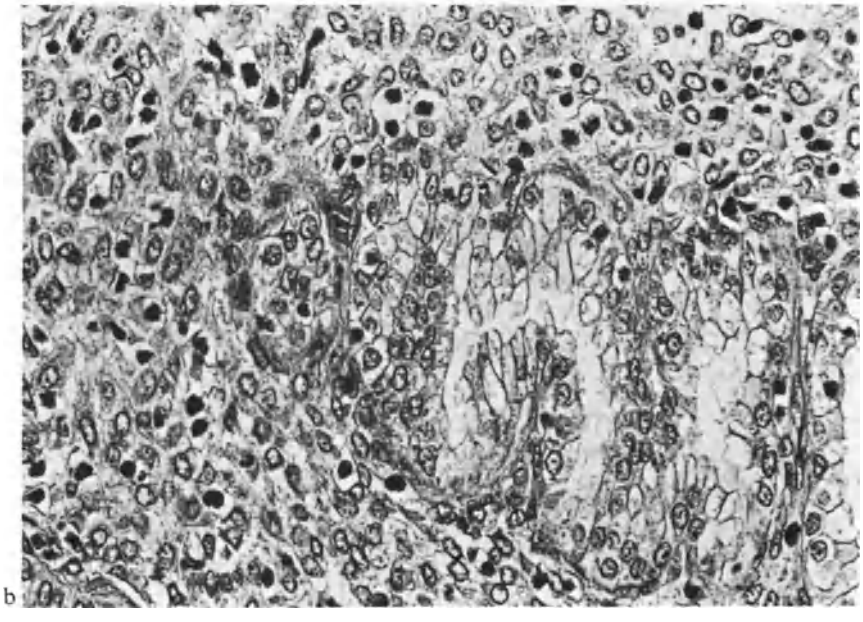


Fig. 27a and b. The thirteenth day after ovulation. Pronounced shrinkage of the glands and stroma with saw-toothed appearance of the glands; the endometrial granulocytes are still numerous. (a) Low magnification. (b) High magnification

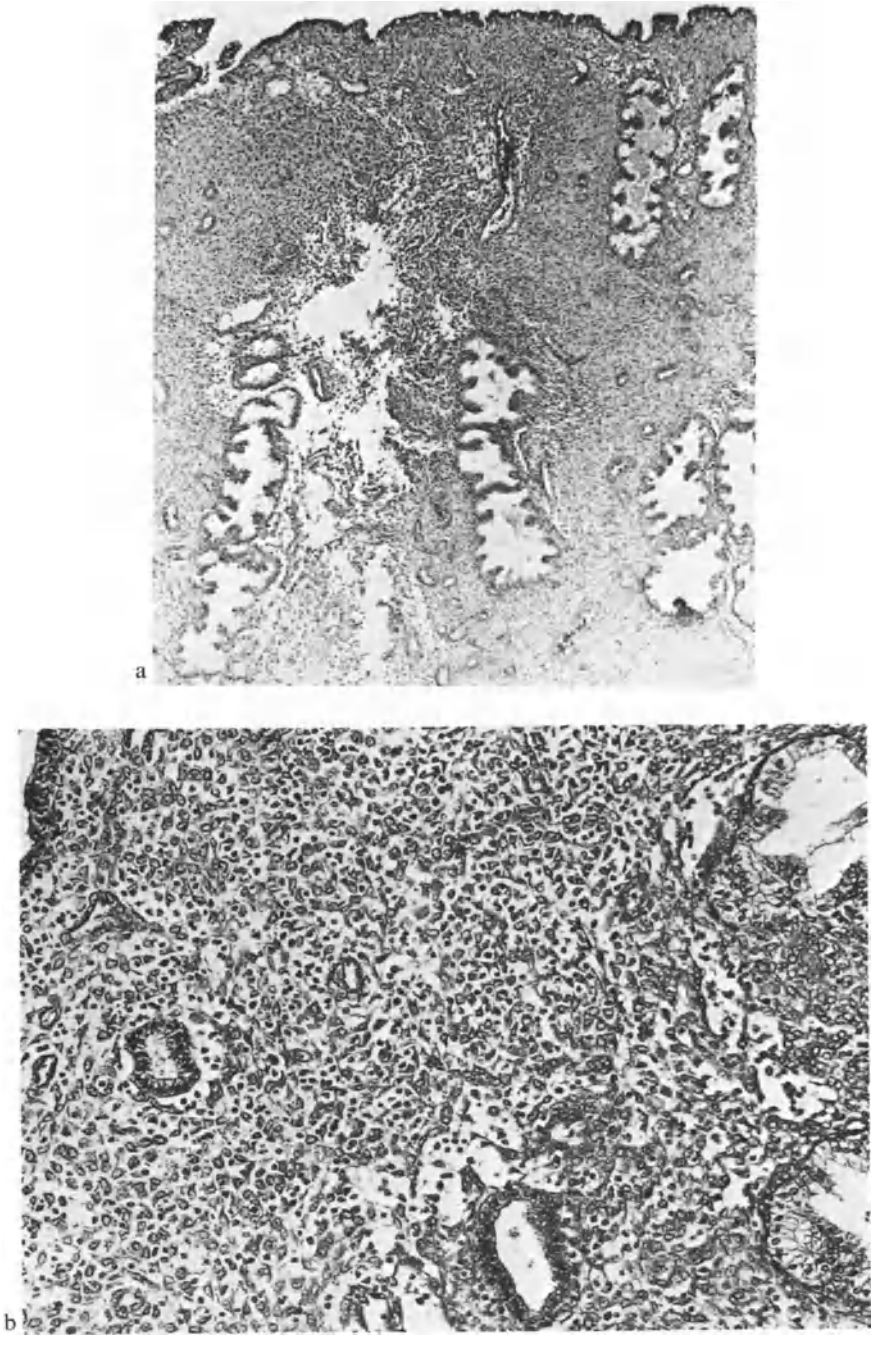
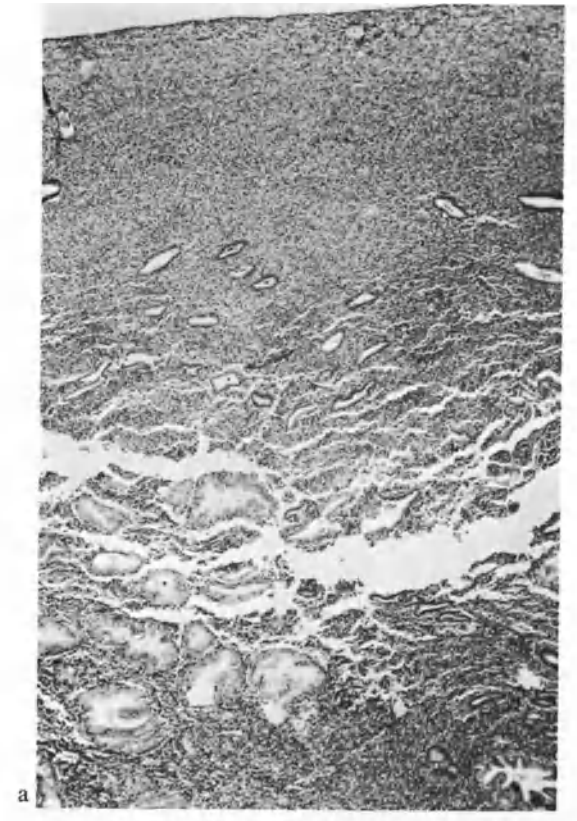


Fig. 28a and b. The fourteenth day after ovulation. Though the tissue in general is intact, dissociation is beginning in the compacta. Onset of release of relaxin from the endometrial granulocytes with dissolution of stromal fibers. Some of the glandular epithelium is markedly shrunken. (a) Low magnification. (b) Higher magnification



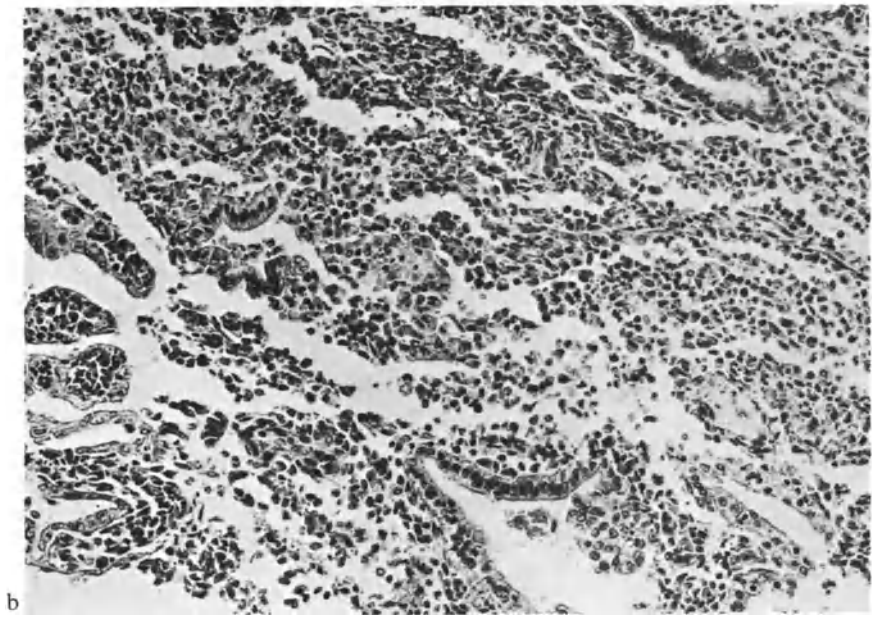


Fig. 29a and b. First day of menstruation. The compacta separates from the spongiosa. Glands and stroma dissociate. (a) Low magnification. (b) Higher magnification

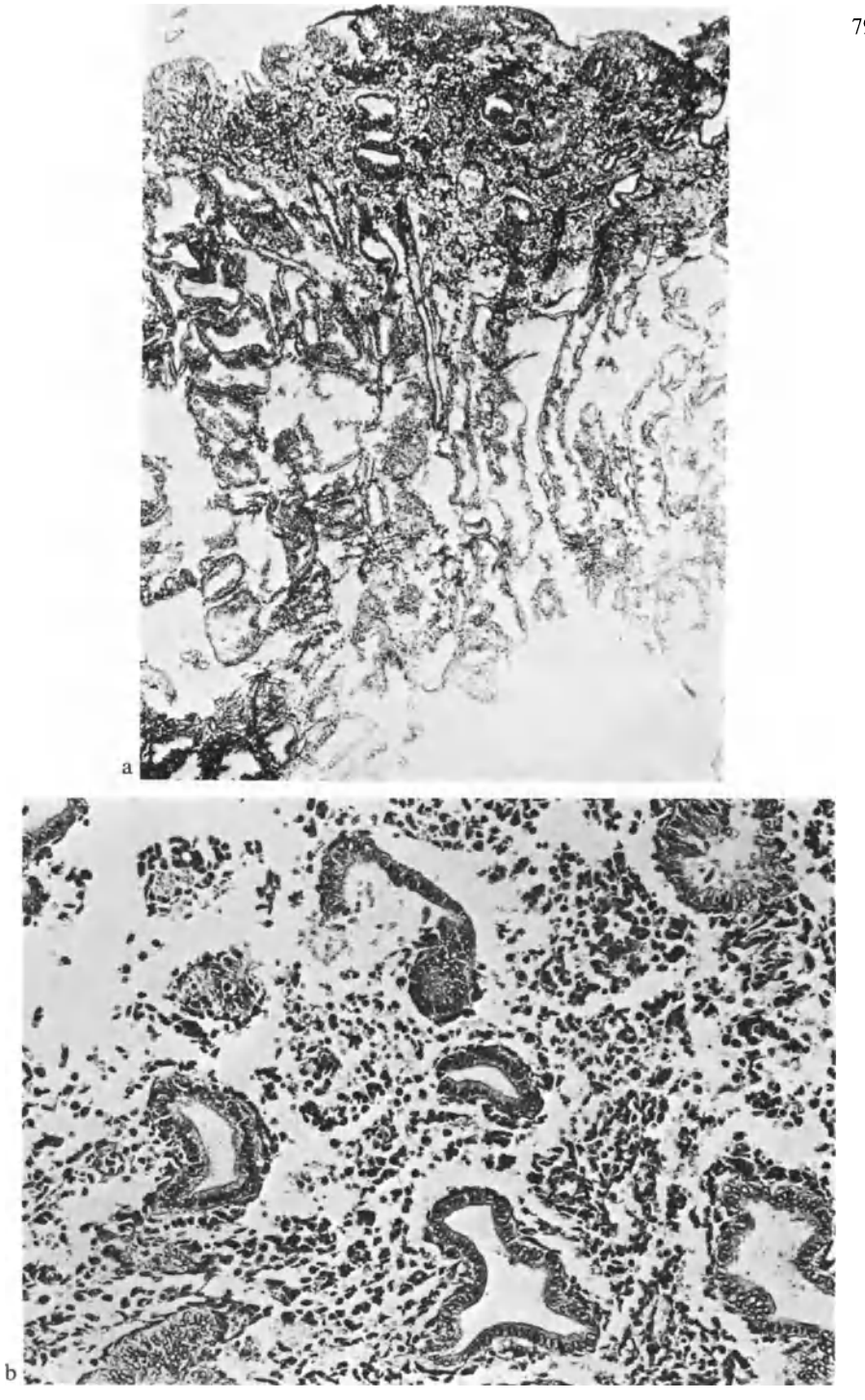


Fig. 30a and b. Second day of menstruation. The disintegration of the tissue is advanced, remnants of collapsed endometrial glands separate from the tissue. (a) Low magnification. (b) Higher magnification

functionalis that remain and are needed for the next cycle. For menstruation to take place in a regular manner, the fall of estrogen and progesterone is essential (ZUCKERMAN, 1949). If their fall is disturbed by any of several possible mechanisms, then menstrual shedding accordingly may be either prolonged or incomplete.

d) Regeneration

Immediately after menstrual shedding ceases and before proliferation begins a **regenerative phase** sets in lasting one to two days, during which the denuded endometrium becomes epithelialized (Fig. 31) The regeneration of the surface epithelium can be readily followed by studies with the scanning electron-microscope (FERENCZY 1976; LUDWIG and METZGER, 1976). It proceeds on the one hand from the stumps of glands in the basalis or lower functionalis. From these the epithelial cells form collar-like aggregates that spread out in all directions. On the other hand, the epithelim remaining in the tubal recesses and isthmus grows out over the adjacent defects. Stromal cells do not take part in the regeneration. Since the newly formed epithelial cells fail to show mitoses, although the synthesis of nuclear DNA and cytoplasmic RNA are increased, cellular proliferation is thought to come about by endomitotic processes (FERENCZY, 1976). Generally, re-epithelization is completed by the fifth day of the cycle, independent of hormonal stimuli. When estrogen stimulation is increased, however, as for example with glandular-cystic hyperplasia, the regeneration is accelerated. As one might expect, the onset, progress, and duration of regeneration vary from patient to patient, just as do the manner and extent to which the endometrium is shed during menstruation (NOGALES *et al.*, 1969, 1978).

e) Possible Variations in the Endometrium During the Normal Cycle

The sequence of changes just described that take place in the endometrium from day to day occasionally fail to develop in all parts uniformly. If extreme differences are evident with variations exceeding two days, then the changes are clearly not normal and a functional disturbance exists. Such endometria are impossible to date accurately.

Here we are primarily interested in the possible deviations that may take place in the height of normal endometrium, in the abundance of its glands, and in the shape of its glands (BEHRENS, 1953; WINTER, 1955). Fully-developed and normal secretory endometrium may vary from 1–10 mm in *height,* depending primarily on the amount of fluid in the stroma. The height of the basalis or the number of glands in it that fail to participate in the cyclic changes may likewise show great differences from patient to patient, or may vary from one part of the endometrium to another, particularly when focal hyperplasia develops in the basalis. Further, although still within normal limits, the boundary between the basalis and the myometrium may be very irregular, simulating at times adenomatous hyperplasia. In like manner, the surface of the endometrium may be wavy, nodular or folded owing to local variations in the content of fluid or glands but without an overgrowth of glands or collagenous fibers that

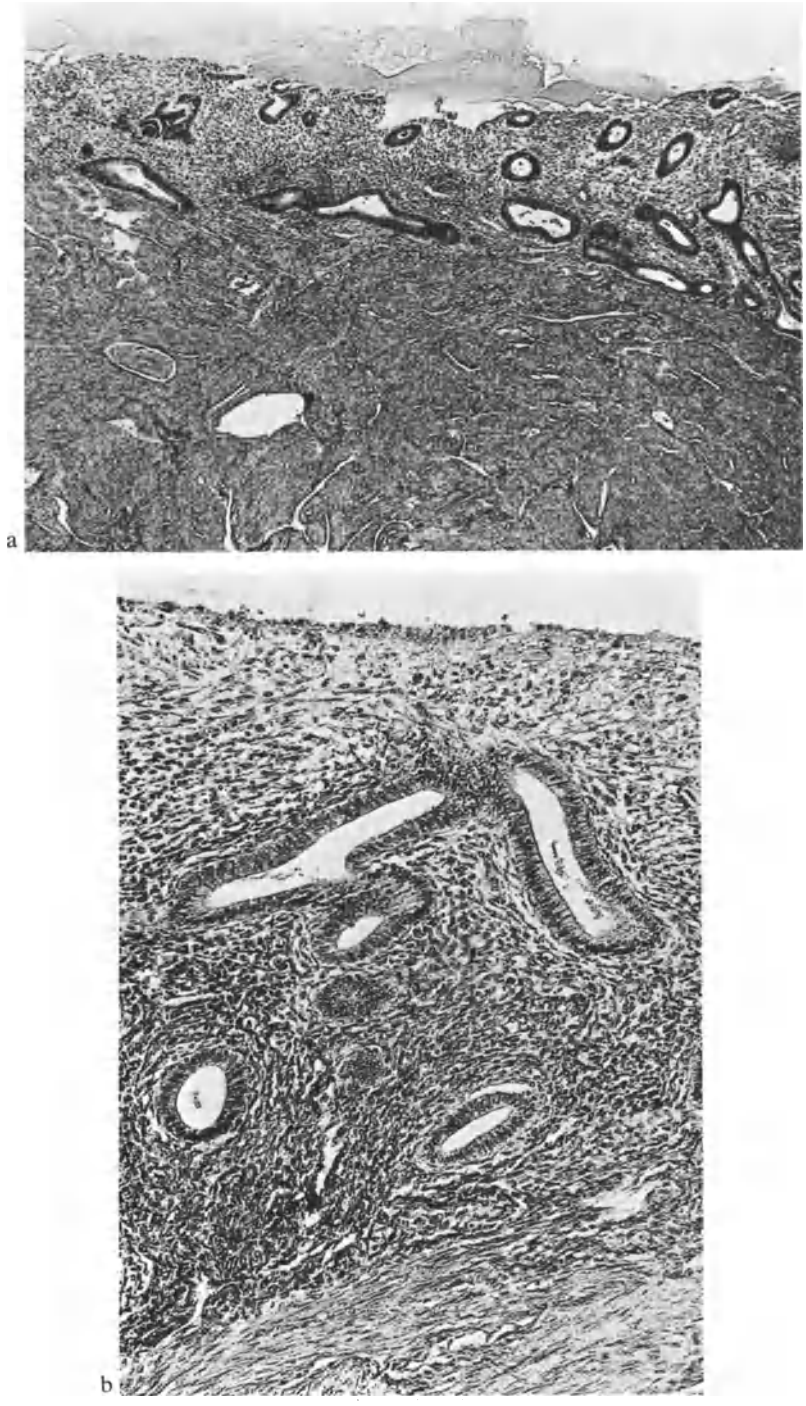


Fig. 31. (a) Onset of regenerative phase after menstruation ceases (low magnification). (b) High magnification: beginning local regeneration of surface epithelium

characterizes polyps. A circumscribed or generalized *paucity of glands* in the functionalis may arise from a comparable scarcity in the basalis. Both deficiencies should be regarded as variations within the range of normal, although the glands that are present may overproliferate, dilate, and grow irregularly. In addition, a localized or generalized *excess of glands* may also develop, even though the glands are normal. *Cystic dilatation* of an occasional gland is not necessarily a sign of focal hyperplasia (WILSON and KURZROK, 1938). When the surrounding stroma is unusually loose or when the flow of glandular secretions becomes obstructed, the glands may enlarge; the change however should not be misinterpreted as a functional deviation. The distinction can easily be made if the glandular epithelium fails to show the changes characteristic of a functional disturbance (Fig. 32a, 33). *Sporadic glands without secretory activity* may occasionally be found at the height or end of the secretory phase, located incongruously among the otherwise homogeneous, actively secreting glands; such inactive glands apparently represent local unresponsiveness to hormonal stimuli, a variation belonging within the range of the biological norm. It is of no pathological importance (Fig. 32b).

7. The Endometrium in the Climacterium and after the Menopause

An increasing frequency or persistence of irregular cycles portends the approaching end of the reproductive period. Slight irregularities in the hormonal balance, indicating ovarian function is waning because of age, may still be within the range of normal yet cause the endometrial glands to proliferate irregularly. At times an insufficient corpus luteum results in imperfectly developed secretory changes. Ovulation may recur sporadically, even years after a menopause; the associated corpus luteum is insufficient (NOVAK, 1970). In addition, a local alteration of endometrial reactivity to estrogen or gestagen may develop owing to climacteric ageing of the endometrium. The arrangement of the glands, their spacing and growth pattern, the width of their lumina, and the height and maturity of their lining epithelium may all vary markedly without these changes implying that a functional disturbance, such as a circumscribed or diffuse glandular-cystic hyperplasia or adenomatous hyperplasia, is present (Fig. 34). We refer to endometria with these changes, therefore, as the preclimacteric or *climacteric transitional type;* we find it occurs in almost 50 per cent of all endometria studied in the climacteric age-group. Some patients with endometria of this type will already have anovulatory cycles when first seen (BEHRENS, 1956). Anovulation can be easily diagnosed, even in the first half of the cycle, if the endometrium is examined with the acridine orange fluorochromation method. Such studies will show that the cytoplasm of the superficial stromal cells fails to fluoresce red, as it should in a normal cycle. Consequently, there is no distinction into two layers (superficial red staining stromal cells rich in RNA; poorly stained stromal cells of the lower half of the functionalis deficient in RNA) characteristically seen at that time in a normal menstrual cycle of the reproductive period. We can also detect an anovulatory cycle or an irregular proliferative phase of the preclimacterium by the absence of the glycogen granules, which normally appear just before

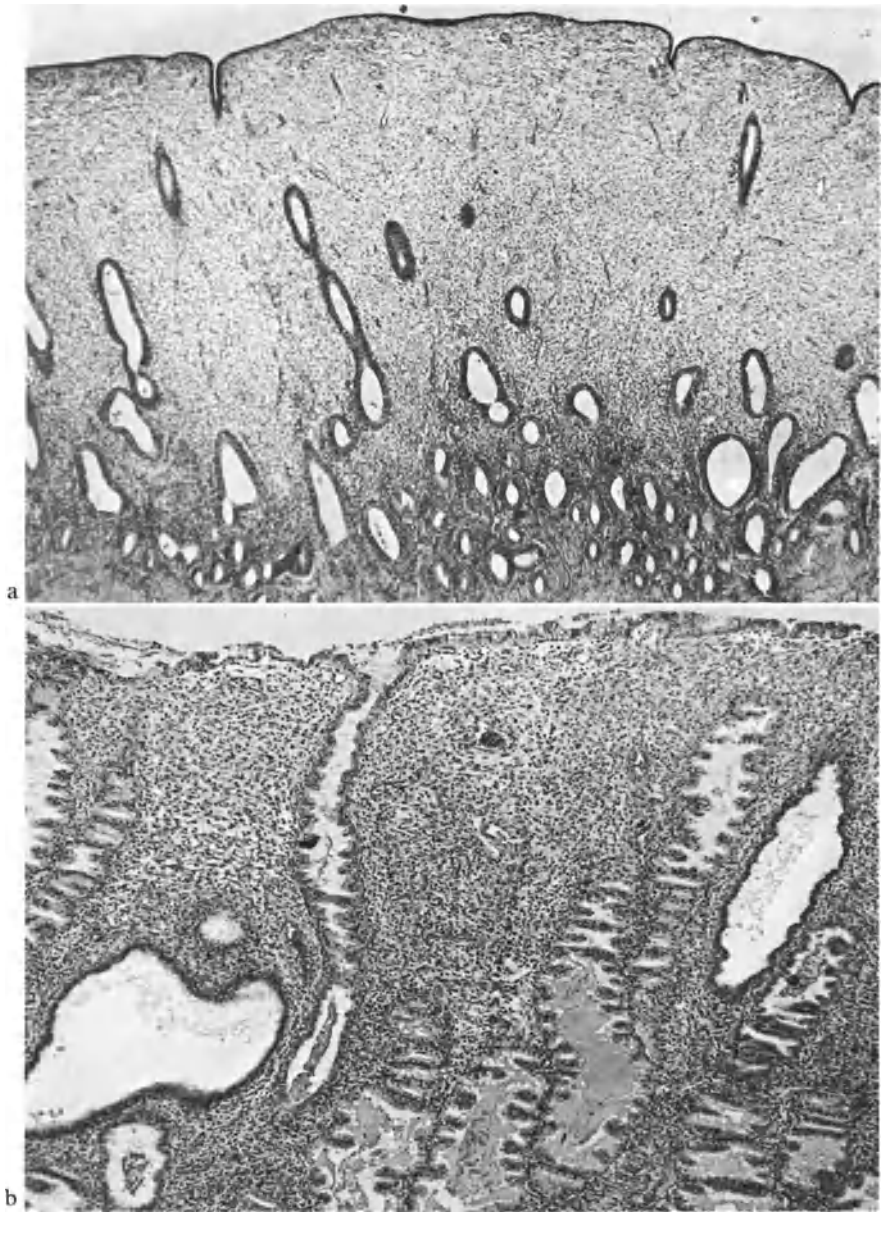


Fig. 32a and b. Physiological variations in the forms of glands; single dilated glands among those of normal size. (a) Beginning proliferative phase. (b) Late secretory phase

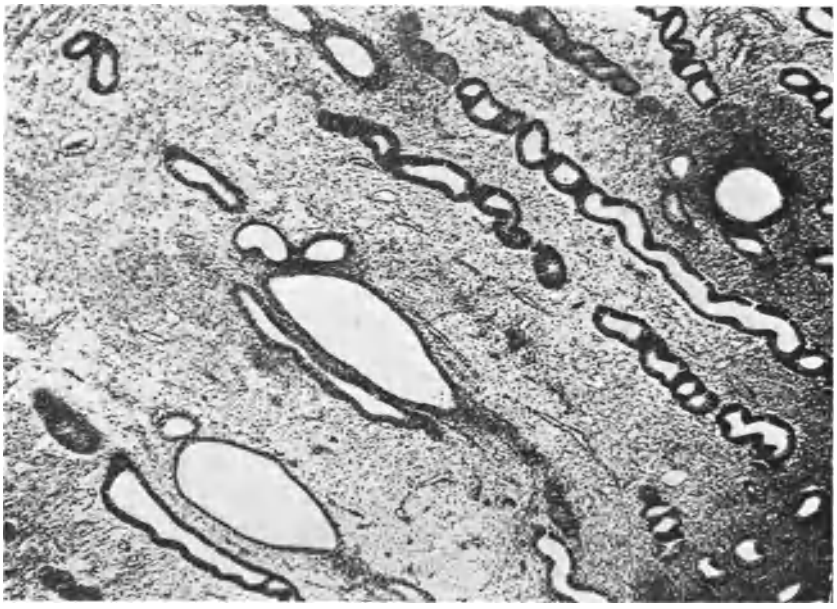


Fig. 33. Elliptical dilatation of the mid-portion of a gland as a physiological variation, mid-proliferative phase

ovulation in the basal parts of the glandular epithelium. For such studies we recommend frozen sections prepared with the cryostat and stained with either acridine orange or the PAS reaction.

After the physiological decline of ovarian function and the sharp fall in the secretion of both progesterone and estrogen, the resting, afunctional endometrium that evolves after the menopause[1] ends as an atrophic endometrium after a few years (see Table 4). Since that atrophic state represents, so to speak, the preserved or "petrified" cycle that existed when the menopause set in, it may have many forms. If the last cycle were ovulatory and ended with a regular menstruation, then a *simple atrophy* will develop with sparse remnants of narrow glands lined by a low epithelium with small inactive nuclei and supported by a dense, fibrous stroma of spindly cells (Fig. 35a). Spiral arterioles will be lacking. The functionalis cannot be separated from the basalis. The amount of RNA and the activities of enzymes either are very low or absent (GOLDBERG and JONES, 1956; GROSS, 1964; personal studies). In contrast, if the last cycle or cycles were anovulatory, or if the proliferative phases were irregular, then what we should find after the menopause sets in is the "petrified" state of that last proliferative phase. Because some glands may be cystically dilated, the histological picture found may be misdiagnosed as a glandular-cystic hyperplasia (Fig. 35b). That a *cystic atrophy* is present, however, is evident from the inactive, flattened

[1] The term "menopause" means etymologically: time of the last bleeding. We prefer to hold to that definition and will refer to the period after the last menstrual period as the "postmenopause", often incorrectly designated the menopause.

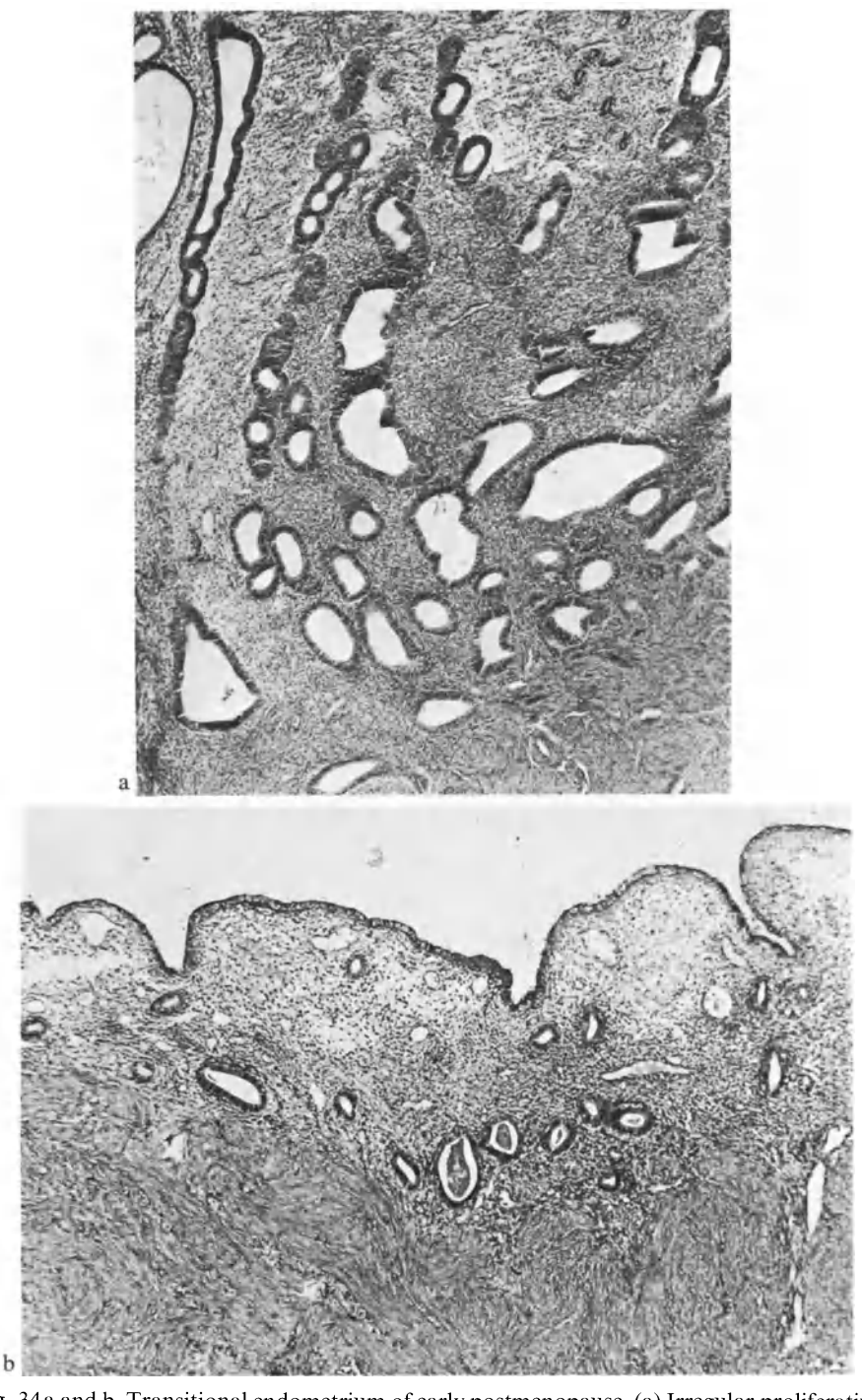
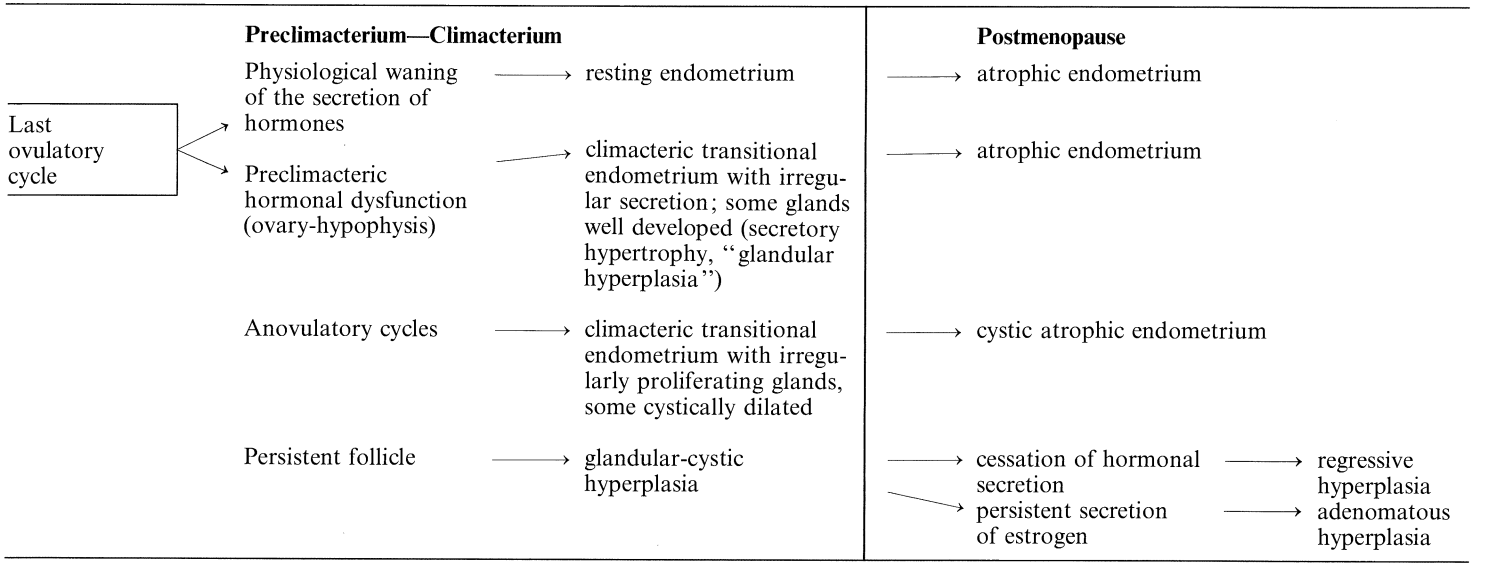


Fig. 34a and b. Transitional endometrium of early postmenopause. (a) Irregular proliferative phase with variation in width of glands, in height of glandular epithelium, and in the density of the stroma. (b) Additional variation in the total height of the endometrium

Table 4. The preclimacteric and postclimacteric endometrium



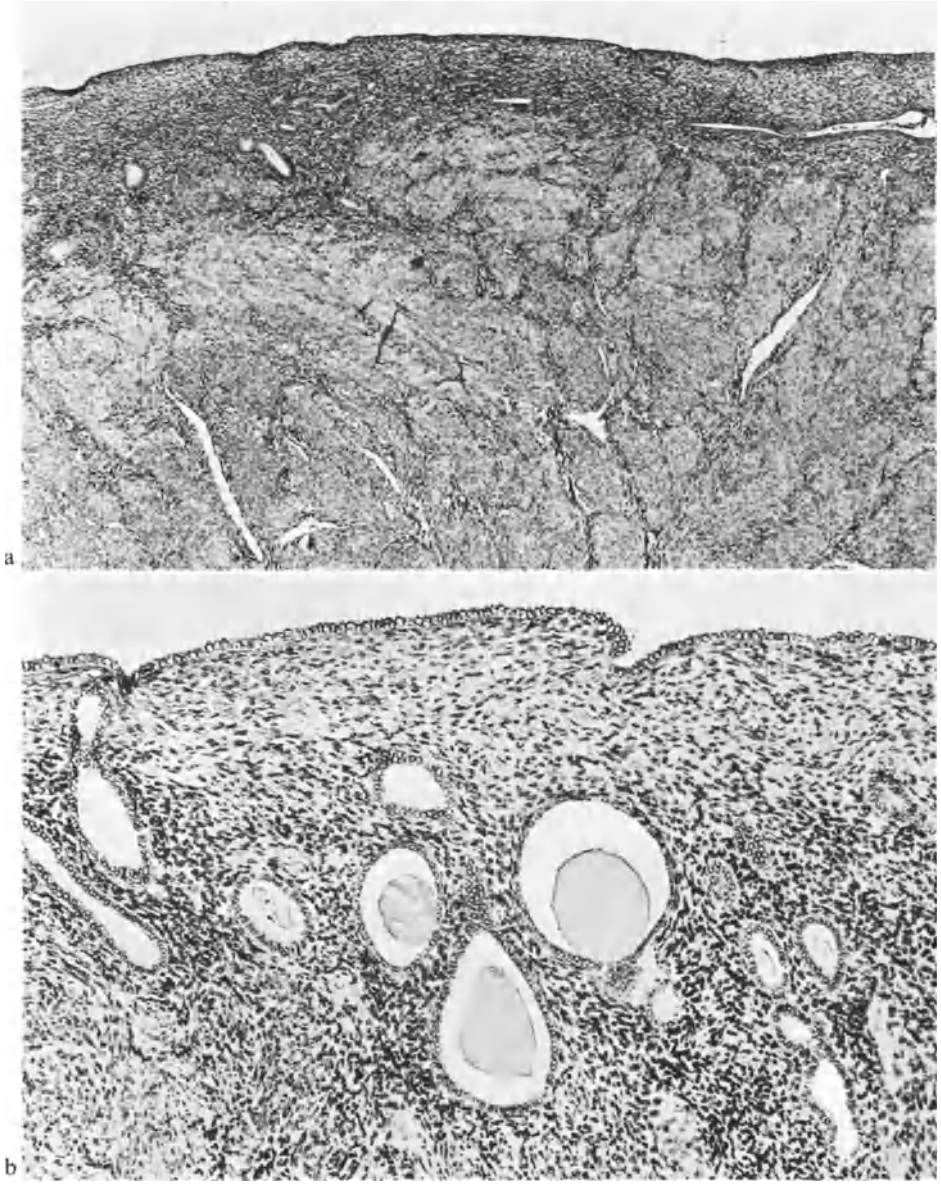


Fig. 35a and b. Physiological atrophy of old age. (a) Simple (b) cystic atrophy

glandular epithelium that contains no enzymes (MANSOUR and BARADI, 1967) and no RNA (MCKAY *et al.*, 1956), as we could show with acridine orange fluorochromation (DALLENBACH and DALLENBACH-HELLWEG, 1968). The stroma is dense, composed of spindly cells devoid of most RNA. The only morphological difference between simple atrophy and cystic atrophy is the diameter of the glandular lumen, but that difference is of no clinical importance. Both conditions

are to be regarded as physiological forms of regression (KELLER and ADRIAN, 1939; SPEERT, 1949; TOTH and GIMES, 1964), of which the cystic atrophy is seen most commonly. According to NOER (1961) it occurs in 76 per cent of all cases, as compared with 7.8 per cent for simple atrophy. In contrast, all other endometrial conditions encountered after the menopause (16.2 per cent) are caused either by an abnormal persistence in the production of estrogen or by treatment with estrogen (BREIPOHL, 1935; NOVAK and RICHARDSON, 1941; HUSSLEIN, 1948; DHOM, 1952; NOVAK, 1953; MCBRIDE, 1954; PARKS *et al.*, 1958). Thus, the proliferation produced should be regarded as pathological; it usually causes bleeding.

C. The Histopathology of the Endometrium

Almost all hormonal dysregulations (that is, endocrinopathies) and organic diseases of the endometrium produce atypical uterine bleeding. Clinically, the cause of the bleeding often remains unclear. Therefore, the attending gynecologist will

Table 5. Causes of atypical uterine bleeding

A. Systemic diseases:

Cardiac and circulatory failure
Hypertension
Blood dyscrasia with thrombocytopenia
Hemophilia, avitaminosis, intoxications, infectious diseases

B. Functional disturbances:

Dysfunction of the ovaries,
pituitary, diencephalon,
thyroid, or adrenal glands
Psychogenic disturbances (cerebral)
Death of extrauterine pregnancy
Hormone-producing ovarian tumors
Exogenous administration of hormones

C. Local anatomic disturbances:

Endometrium: Endometritis
Abortion or retained products of conception
Foreign bodies (talcum powder, intrauterine device)
Polyps
Neoplasms

Myometrium: Vascular anomalies (aneurysms)
Myometritis
Fibromyoma-submucous, intramural, subserous
Adenomyosis
Neoplasms

Portio and cervix: Cervicitis
Polyps
Glandular-papillary erosion
Neoplasms

Structural changes of the vagina, vulva, parametrium
Anomalous positions of the uterus with circulatory disturbances (hemostasis)

☐ Usually can be diagnosed by histological study of curettings.

⬚ Can be diagnosed only at times.

attempt to establish a diagnosis in all his patients with unexplained bleeding by submitting curettings for histological study. Most causes of atypical uterine bleeding can be revealed histologically. The percentage of patients whose endometrial curettings fail to disclose pathological changes is small, varying from 3.6 per cent to 18 per cent, depending upon the investigator who makes the examination (LAU and STOLL, 1963; also for further literature). The cause of the bleeding in that small percentage of women is either morphologically extra-uterine or functionally extra-ovarian (see Table 5).

By carefully correlating the histological study of the endometrium with the patient's anamnesis and the results of clinical tests, and by using special stains and eventually histochemical reactions, it is often possible to diagnose conditions that are unclear in sections prepared by routine methods. At least a presumptive diagnosis can be made at times. For example, a stretched and compressed endometrium may suggest a submucosal leiomyoma, or microaneurysms of the endometrium may mean thrombocytopenic purpura.

In evaluating pathological changes of the endometrium one should consider all the causes for the disturbance that led to curettage. These causes may be divided into three main groups, as shown in Table 5. In the following chapters we shall examine as precisely as possible how each condition of these groups histologically varies from the normal, enabling us then to differentiate the causative disturbances from one another and to reach a definitive diagnosis.

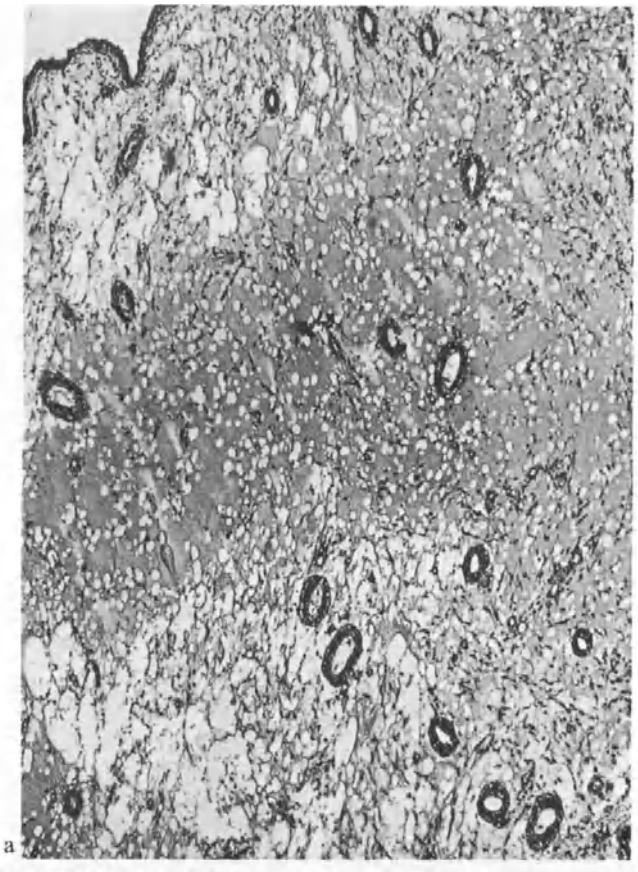
1. Morphological Effects of Circulatory and Coagulation Disturbances

a) Edema

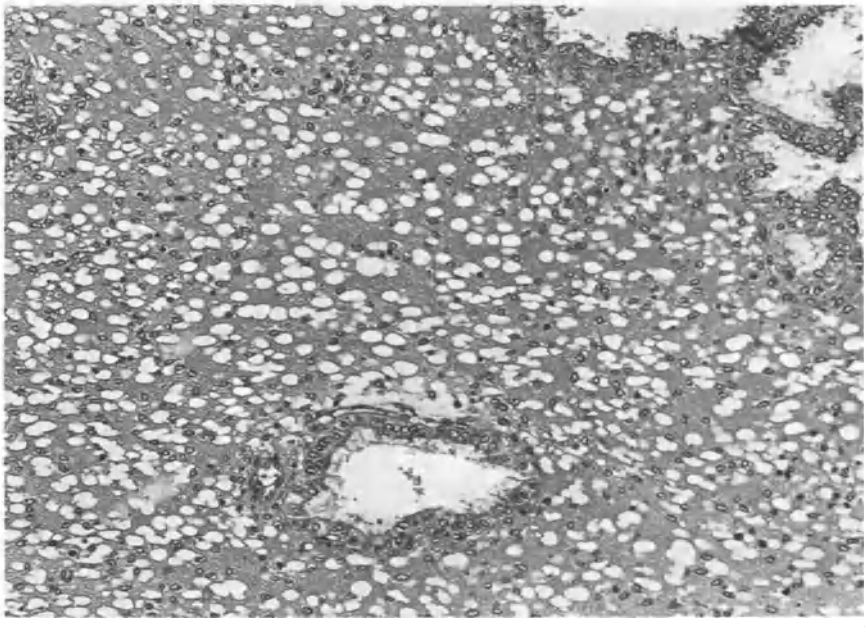
The vascular system of the endometrium is unusually sensitive to fluctuations in levels of the sex hormones and reacts to such variations by promptly dilating; that leads to hyperemia, slowing of the bloodflow, and edema. Similar changes also take place at specific times during a normal menstrual cycle (see Fig. 11). Thus, before one diagnoses a pathologic edema of the endometrium one must determine the phase of the cycle. In our differential diagnosis it is necessary to exclude the physiological edema that develops when the levels of estrogen in the blood are highest; namely, in the middle of the proliferative phase and around the twenty-first to twenty-fourth day of the cycle.

Pathological edema of the endometrium may be traced back to a circulatory disturbance that can be caused either by venous or lymphatic obstruction (increased hydrostatic pressure) or like physiological edema, by hormones (functional abnormality) (DERICHSWEILER, 1934; CRAMER, 1952).

Often in *ovarian dysfunction* only estrogen is secreted; its unopposed action induces focal or diffuse hyperplasia of the endometrium and polyp formation. The stroma of the proliferated regions frequently is extremely edematous; the glands are pushed apart and the reticulum network pulled asunder (Fig. 36). Occasionally small lakes of edema fluid form, as serous exudates seep from the greatly distended vessels, their walls often swollen with hyaline material. Not infrequently we find a distinctly patchy edema of the endometrial stroma of



a



b

Fig. 36a and b. Pathological edema of the stroma; the stromal cells are pushed widely apart and the reticulum fibers are sparse. (a) Low magnification. (b) Higher magnification

women who are taking oral contraceptive agents (see p. 228). Its uneven character is comparable to the diversity of changes we see in the neighboring glands and stromal cells, which disclose marked disparity in their development. We must assume that in these women the changes also represent intense, local variations in the effect of estrogen.

Among the *mechanical causes of increased hydrostatic pressure* are: changes in the position of the uterus, leiomyomata, and polyps. In a retroflexio uteri the pressure in the capillaries may simply be increased by venous or lymphatic

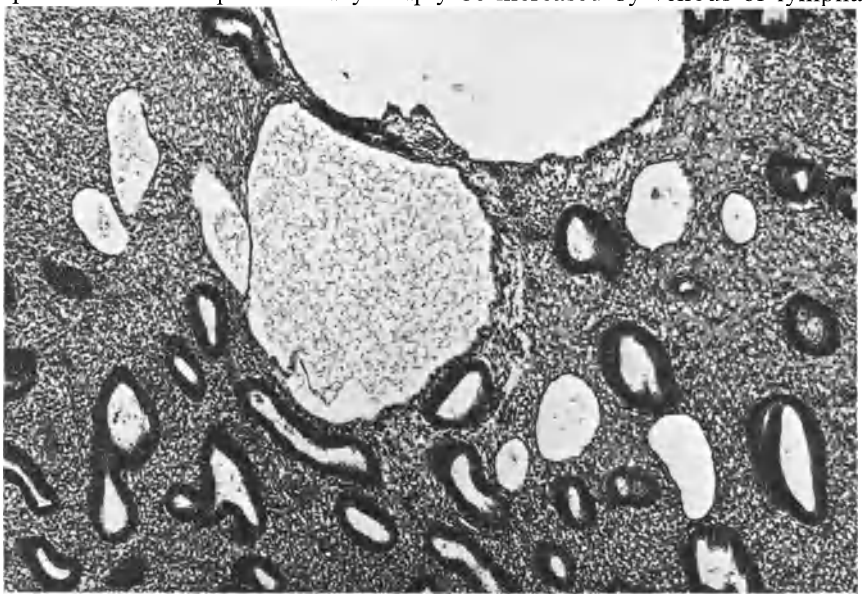


Fig. 37. Cystic lymphatic channels of various sizes in the lower functionalis. Their flattened lining of endothelium can readily be distinguished from glandular epithelium

obstruction. Submucous myomata may lead to local disturbances of the circulation by stretching or compressing endometrial vessels (HEINICKE, 1959). During hysterectomy ligation of the blood vessels may obstruct lymphatic channels. Depending on how long the operation lasts, the blocked endometrial lymphatics dilate, and in extreme cases form cysts which may be mistaken for dilated endometrial glands. The cystic lymphatics can be distinguished by their lining of flattened endothelial cells (Fig. 37).

b) Chronic Passive Hyperemia; Hemorrhage Caused by Extragenital Diseases

The causes that induce a pathological edema may also give rise to chronic passive congestion. If bloodflow in the vessels stops (stasis), then the walls of the vessels become injured, and as injury progresses the walls may leak not only edema fluid but blood cells as well. Mild but protracted bleeding follows. Chronic passive hyperemia with hemorrhages in an otherwise normal endometrium may be a sign of cardiac failure. In contrast, a hemorrhagic infarct of the endometrium from venous thromboses is extremely rare.

The term *apoplexia uteri* refers to a diffuse hemorrhage of the endometrium caused by chronic passive hyperemia. We see it most often in old women afflicted with sclerosis of the uterine arteries and generalized arteriosclerosis. Most of the patients have either an organic or functional disturbance of the heart and circulatory system (DALY and BALOGH, 1968). Some facts suggest, however, that apoplexia uteri is nothing more than an agonal hemorrhage after inadequate circulation in a vascular system already impaired by arteriosclerosis (TERASAKI, 1928). It is usually encountered incidentally at autopsy. We also see it occasionally in the uteri of older women that were removed by vaginal operation. In these

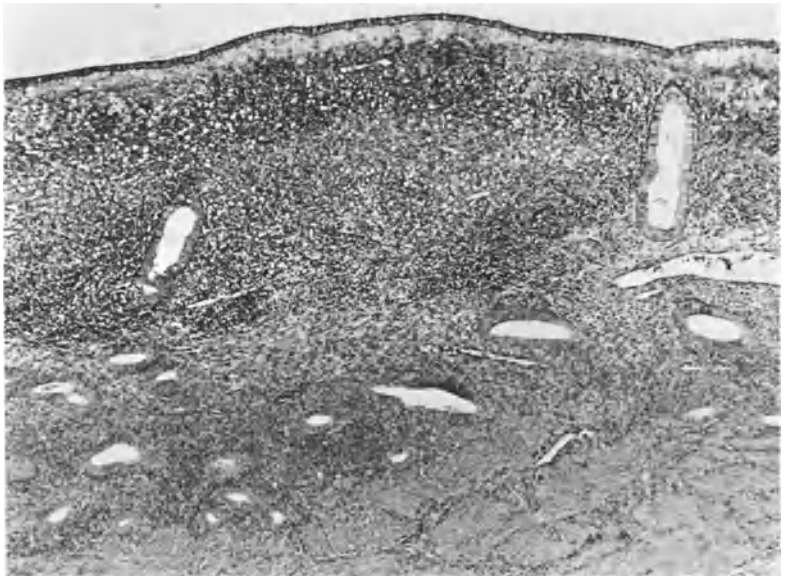


Fig. 38. Apoplexia uteri: Hemorrhage into the upper stroma of a resting endometrium

instances besides the vascular disease the operative trauma is important in causing the endometrial hemorrhage. Grossly, the hemorrhage confines itself to the endometrium and ends sharply at the internal uterine os. Histologically, the striking feature is the widespread extravasation of blood throughout the superficial endometrial stroma (Fig. 38). One occasionally finds small aggregates of polymorphonuclear leukocytes about scattered, focal necroses. Hemosiderin-filled macrophages are absent; therefore, the hemorrhage has not been present long.

Menorrhagia due to extragenital disease may occasionally develop in severe infections, poisonings, avitaminoses, or in blood dyscrasias that are associated with disturbances of coagulation owing to decreased numbers of platelets, particularly as in *thrombocytopenia* (HALBAN, 1922; GOECKE, 1932; GREMME, 1932). A thrombotic thrombocytopenic purpura may lead to a severe menorrhagia (SYMMERS, 1959; "thrombotic microangiopathia"). Histologically, the involved vessels are dilated; some reveal microaneurysms; others are partially occluded by a thrombus covered with endothelial cells. In our differential diagnosis we must

differentiate this condition from the much more common thrombosis of vessels associated with tissue necrosis that develops in a glandular-cystic hyperplasia or after estrogen therapy.

Recently we studied a *pseudomelanosis* of the endometrium that closely resembled intestinal pseudomelanosis. Histologically, the glandular lumina to the level of the spongiosa were filled with old blood, which in the central parts had been converted into hemosiderin. The patient had been taking oral contraceptive

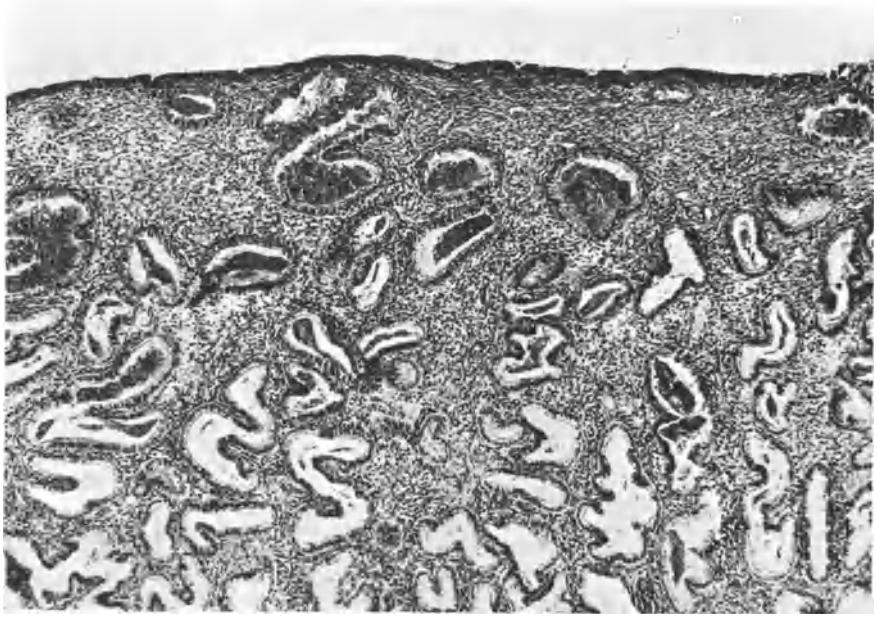


Fig. 39. Pseudomelanosis of the endometrium. The portions of glands near the surface are distended and filled with old blood

agents; these, it seems, had brought about persistent withdrawal bleeding without dissolution or shedding of the endometrium. Blood had simply seeped into the glandular lumina (Fig. 39).

No matter what their etiology may be, if pathological hemorrhages occur when the isthmus, cervical canal, or cervical os are stenosed, then a *hematometra* develops, and the superficial layers of the endometrium imbibe blood (Arrata and Zarou, 1963). If the hematometra persists then the resulting pressure and distention may cause the endometrium to atrophy.

2. Functional (Hormonal) Disturbances

Of the several target organs for the ovarian hormones, the endometrium, without doubt, is the most sensitive indicator of ovarian function. It promptly responds to every disturbance in ovarian hormonal balance that may develop from either

absent, deficient, or excessive function of the ovarian cells which secrete the hormones. The morphological changes produced in the endometrium will vary greatly, depending on in what stage of maturation a follicle becomes injured. In the following we want to review what happens in the endometrium when the follicle becomes arrested at various stages of its maturation.

a) Atrophic Endometrium from Non-Functioning Ovaries

If in the childbearing age both ovaries are excised or functionally eradicated (for example, by x-irradiation, by chemical toxins, or by damage of the controlling

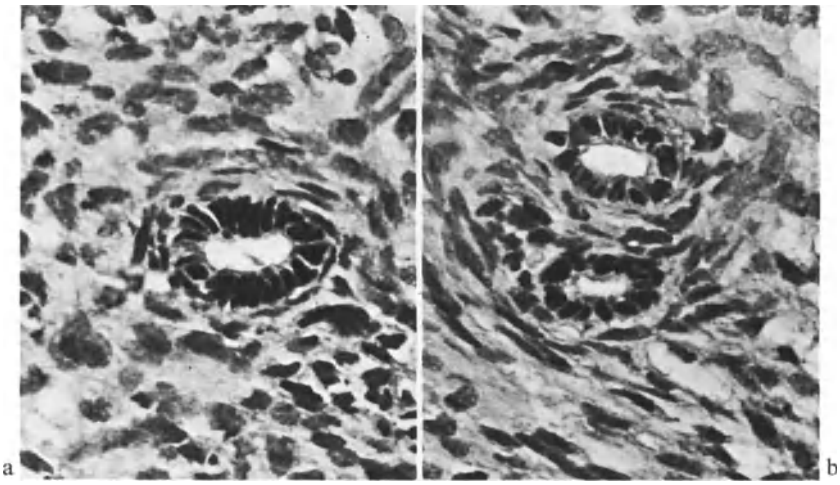


Fig. 40a and b. Endometrium from patient without ovarian function. (a) Resting glands. (b) Atrophic glands

centers in the hypothalamic-pituitary system), then the endometrium receives no hormonal stimulus and remains in a functionless, resting phase. If that resting phase persists, the stroma and glands continue to atrophy and disappear since as non-functioning components of tissue they are gradually absorbed. Histologically and histochemically the atrophic endometrium of castration resembles the physiological atrophy of the endometrium seen before puberty or after the menopause. Its narrow glands are extremely sparse and lined by low cuboidal epithelial cells with small, round nuclei of dense chromatin. Their cytoplasm is scanty (Fig. 40b). Mitoses are lacking. The stroma consists of small, densely-packed, spindly cells. The entire height of the atrophic endometrium is equivalent to but a fraction of the original basalis, which now cannot be recognized. In extreme instances no glands remain, and the flat epithelium of the surface is separated from the myometrium by a stromal layer just a few cells thick. The spiral arteries are undeveloped. The glandular and stromal cells contain little RNA, alkaline or acid phosphatase. Glycogen and glycoproteins are nowhere to be found (GOLDBERG and JONES, 1956; MCKAY *et al.*, 1956; LEWIN, 1961; GROSS, 1964).

In rare instances we see atrophic endometrium associated with normal ovarian function and a regular biphasic menstrual cycle (PLOTZ, 1950; EUFINGER, 1952;

STIEVE, 1952). In these instances the ovarian hormones, although secreted, fail to stimulate the endometrium, apparently because it is refractive to them ("silent ovulation" of STIEVE). Perhaps the endometrial cells are unable to produce estrogen receptors. Instead of menstruation, vicarious bleeding may develop in the adnexae or myometrium.

Independent of the levels of the ovarian hormones, a localized atrophy of the endometrium may be produced by mechanical causes, as for example, by the compressing and stretching from a large submucosal leiomyoma. We refer to this type of atrophy as *pressure atrophy* (Fig. 41), realizing however that the

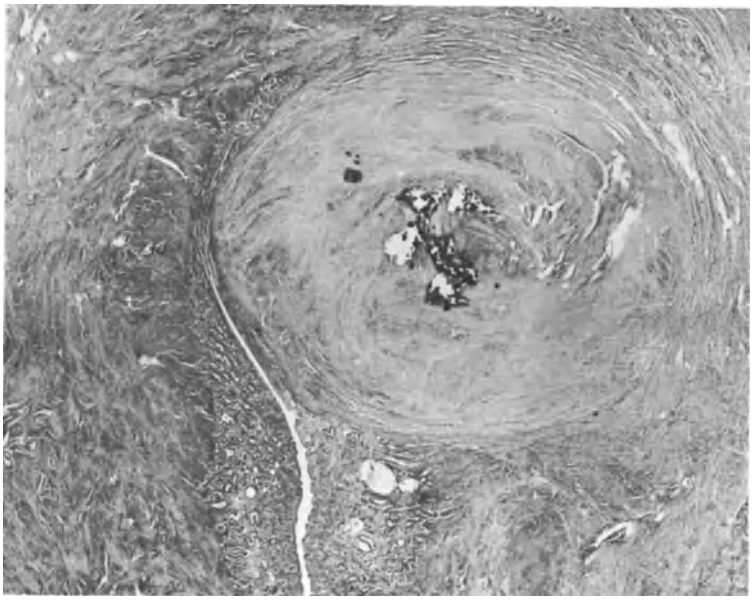


Fig. 41. Pressure atrophy of the endometrium overlying a submucosal leiomyoma. The endometrium of the opposite side also reveals pressure atrophy

cellular changes are not to be distinguished from those seen in atrophy due to lack of hormones. As pressure atrophy is always focal and usually surrounded by rather hyperplastic glands, the coexistence of atrophic and hyperplastic or irregular portions of endometrium in the same curettings may be an aid in diagnosing a submucosal leiomyoma (DELIGDISH and LOEWENTHAL, 1970). Abnormal bleeding in these cases may be due either to pressure necrosis or to mechanical obstruction which causes congestion and dilatation of the overlying venules (FARRER-BROWN *et al.*, 1971).

b) Resting Endometrium Resulting from Inadequate Ovarian Function (Ovarian Insufficiency, Hypofolliculinism)

Clinically, we expect to find a resting endometrium when the ovaries are underdeveloped (hypoplastic, rarely polycystic), and when the hormones they produce are insufficient for the endometrial buildup and differentiation of a normal cycle.

Another cause for a resting endometrium is a recent but complete arrest of ovarian function. If the ovaries remain inactive, then the resting phase further regresses into an atrophy. Hence, the resting endometrium may represent on the one hand a transitional stage; on the other hand, it may indicate ovarian insufficiency with hypofolliculinism (hypoestrogenism).

Histologically, the resting endometrium has more glands than the atrophic endometrium, a characteristic we use to differentiate the two conditions. The glands are narrow, lined by a single row of columnar epithelial cells (they rarely are stratified) with chromatin-rich, oval nuclei that lie close together in scanty cytoplasm (Fig. 40a). The cells of the stroma are spindly and in general densely packed but may at times be dispersed by edema fluid. Mitoses are very rare. Both glandular and stromal cells contain little RNA; their enzyme activities generally are also low. The height of the resting endometrium may vary but its maximum is 3 mm. Because the sub-threshold amounts of estrogen remain inadequate for inducing a regular proliferation, the processes of regression soon counterbalance those of growth.

Clinically, an amenorrhea or hypomenorrhea almost always accompanies an atrophic or resting endometrium. An exception is the endometrial bleeding in senile atrophy that may develop secondary to apoplexia uteri associated with hypertension (STOLL and BACH, 1954), myometrial arteriolosclerosis (MEYER *et al.*, 1971) or mechanical vascular obstruction by submucosal leiomyoma or uterine prolapse. On the other hand, the question whether we will find an atrophic or resting endometrium with every amenorrhea or hypomenorrhea should be answered with no (see Table 6). Some women experience no menstruation though

Table 6. Histological and clinical results in the various types of amenorrhea

Ovary	Endometrium	Menstruation	Basal temperature	Sterility
▌atrophic	atrophic	none	monophasic	yes
normal	▌atrophic	none	biphasic	yes
normal	biphasic	▌none	biphasic	no

▌= stimulating effect of hormone blocked.

their ovaries function normally, and their endometrium develops a secretory phase like that of a normal cycle (TEN BERGE, 1936; LAUTERWEIN, 1941; PLOTZ, 1950; HOFFMANN, 1951; BENGTSSON and INGEMANSSON, 1959; PHILIPPE *et al.*, 1966). In primary[2] or secondary[3] amenorrhea all that happens at the end of the menstrual cycle is the functionalis contracts intensely. LAUTERWEIN histologically found a secretory endometrium in 13.7 per cent of his patients with amenorrhea; PLOTZ reported the same phase in 15 per cent of his amenorrheic patients. In the histological and histochemical studies of the endometrium from 221 women with oligoamenorrhea, MYRHE (1966) diagnosed an atrophic endometrium 47 times, a resting endometrium 26 times, and a hyperplastic endometrium 5 times;

[2] In primary amenorrhea—the patient has never menstruated.

[3] In secondary amenorrhea—the patient ceases to menstruate after having had menstrual bleeding, which may have been either regular or sporadic.

52 of the women histologically were in the early proliferative phase, 24 in the late proliferative phase, and 19 in the secretory phase. In 48 instances the biopsy specimen was inadequate for histological diagnosis. The greater the endometrial atrophy the lower the levels of estrogen in the urine. In a study of a large group of women with functional amenorrhea, WALLAU (1948) histologically found an atrophic endometrium in only 6.4 per cent. Occasionally a persistent corpus luteum may cause secondary amenorrhea, since with the greatly retarded fall in progesterone the decidualized endometrium undergoes functional hypertrophy (socalled pseudopregnancy).

Histological studies of endometrial biopsies (single stroke, "strip" specimens) from patients with hypomenorrhea often disclosed a normal endometrium. In 75 per cent of such patients (PLOTZ, 1950), however, only the superficial endometrium desquamated, the remaining endometrium merely contracted (HOFFMANN, 1947). The histological appearance of these endometria may so closely resemble irregular shedding of the endometrium of quite a different cause (persistent corpus luteum, see p. 134) that the two conditions may be confused with one another. Here the pathologist is dependent on exact clinical information before he can make a correct functional diagnosis. Since high doses of estrogen fail to provoke withdrawal bleeding in these hypomenorrheas or amenorrheas of similar cause (HOFFMANN, 1951), we must assume that because the endometrium lacks certain factors it is unable to shed properly. In spite of persistent primary amenorrhea, this type of cycle need not be sterile (secretory changes do develop) and pregnancy may take place; the correct diagnosis therefore is of great prognostic importance for the patient. Consequently, in all patients with amenorrhea of unclear etiology an attempt should be made to explain the amenorrhea by histological studies. Because the subject is so complicated I must refrain from discussing the clinical problems and various forms of primary and secondary amenorrhea or their etiological mechanisms. I refer the interested reader to standard texts of clinical gynecology and gynecological endocrinology.

c) The Endometrium Associated with a Persistent Follicle

If LH fails to rise after the follicle has normally matured, then ovulation does not take place. The unruptured follicle may either become atretic forthwith or regress after a few days (persistent follicle). As the estrogen gradually decreases, withdrawal bleeding sets in about fourteen days later when menstruation would normally start, and the anovulatory cycle ends. With the maturation of a new follicle, ovulation may take place, followed by a regular menstruation. If anovulation occurs again, then with every subsequent persistence of a follicle a chain of anovulatory cycles may develop. With a prolonged persistence of a follicle, however, the sustained secretion of estrogen from the persisting follicle and from any newly ripening follicles may induce the endometrium to undergo a glandular-cystic hyperplasia.

α) **The Anovulatory Cycle,** described by MAZER and ZISERMAN in 1932, and NOVAK in 1933, occurs predominantly at the beginning and end of the childbearing age (DÖRING, 1963). It is the second most common cause of sterility, accounting for 6.9 per cent (DÖRING, 1968) to 13.6 per cent (OVERSTREET, 1948). HAMMER-

STEIN (1965) distinguished three types of anovulatory cycle based on how high and how long the secretion of estrogen persists. In the first type A, the follicle continues to secrete for about 7–10 days. In the second type B, an additional secretion of gonadotropin takes place with little luteinization of the follicle. In the third type C, the follicle becomes insufficient early and the estrogen levels remain low. The duration of the anovulatory cyle may vary, depending on whether the atresia of the follicle begins early or late. At times the interval between the withdrawal bleedings is shorter than between the menstruations of normal cycles. Often the interval is longer. In general, the follicles that persist for a short time are more common than those that undergo premature atresia. In general, the concentrations of receptors for estrogen and progesterone correspond to those of the late proliferative phase. Only the concentration of the intranuclear progesterone-receptor, however, is lower than that of the preovulatory endometrium, a finding which correlates with the very low levels of plasma progesterone.

As we should expect, commensurate with the waxing and waning of the hormone levels, the histological picture of the endometrium also fluctuates: all histological stages may be found, from atrophy to hyperplasia (NOVAK, 1940). The most important criterion for making the diagnosis from curettings is the absence of secretory changes in the second half of the cycle. In contrast, the first half of the cycle differs little from the proliferative phase of a normal cycle. Consequently, if an anovulatory cycle is suspected, then the curettage should be performed during the second half of the cycle, and when possible, just before the onset of the expected bleeding or at its onset. Absence of secretory changes in the third week, however, may also result from a prolonged proliferative phase and subsequent delay in ovulation. If during the last days of the cycle or at the onset of bleeding one finds a proliferating endometrium that resembles either the early, middle or late proliferative phase, then with corroborating clinical data (known day of the cycle, monophasic curve of basal temperatures) and with convincing results of cytological studies (estrogen smear) one can diagnose an anovulatory cycle. SEDLIS and KIM (1971) described a band of collagen beneath the surface epithelium in 17 per cent of their infertility cases. The band was associated only with anovulation; its diagnostic significance, however, has been questioned in further investigations (AGRAWAL and FOX, 1972). In contrast to a normal proliferative phase and a glandular-cystic hyperplasia, the endometrium of the fourth week of an anovulatory cycle shows no activity of alkaline phosphatase (ATKINSON, 1950), since the level of estrogen has already decreased. From the degree of proliferation, however, it is possible to infer how high the level of estrogen still is. If it has fallen, then we often find focal hemorrhagic necroses or fresh hemorrhages in the stroma without dissolution of the reticulum fibers or dissociation of the stromal cells. On the other hand, if a follicle persists for a short time and continues to secrete estrogen, then occasional glands scattered among the normal proliferating glands undergo cystic dilatation. At times small amounts of glycogen become evident in the glandular epithelium. These deposits indicate that the persistent follicle underwent a limited and deficient luteinization, possibly because of abnormal hypophyseal regulation. Other proliferative endometria of an anovulatory cycle may also disclose sporadic, focal secretory changes

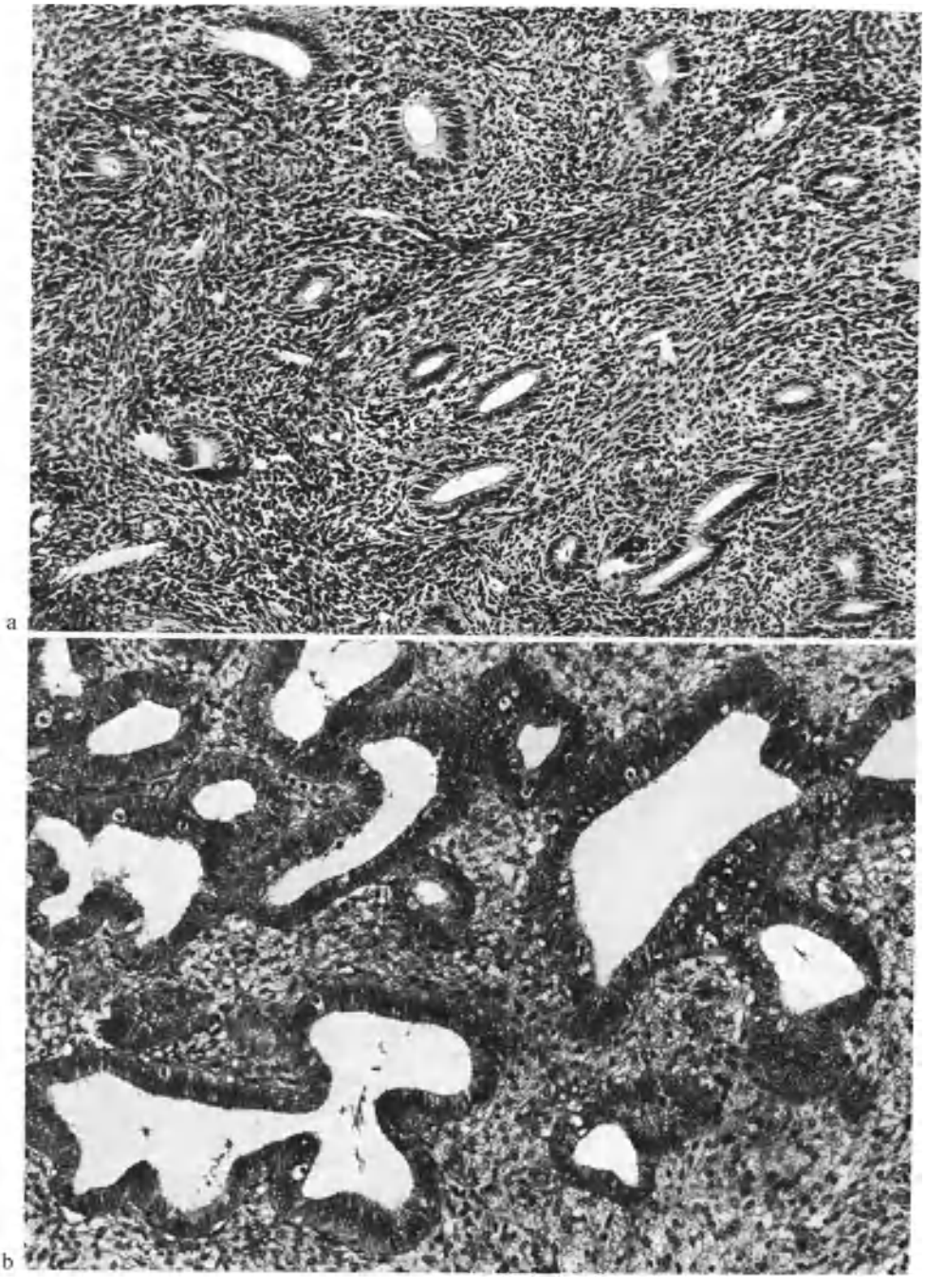


Fig. 42a and b. The different forms of an anovulatory cycle. (a) Deficient proliferation due to follicular insufficiency. The glands are sparse, narrow, their proliferation retarded. (b) Irregular proliferation due to a persistent follicle: glands variably dilated, convoluted, their proliferation pronounced. Magnifications in (a) and (b) the same!

induced by similar hypophyseal centers but no evidence that ovulation took place. These unusual endometria prompted PLOTZ (1950) to distinguish them as an "intermediate type" within the spectrum of the anovulatory cycle.

Because of the practical and therapeutic advantages attained, the anovulatory cycle has been divided into two histologic patterns readily distinguished from one another: 1) the deficient proliferation, 2) the irregular proliferation.

Compared with those of the normal proliferative phase, the glands and stroma in the *deficient proliferation* remain clearly retarded. The glands are slender and straight. The height of the endometrium is only moderate (Fig. 42a). The cause of the anovulation is follicular insufficiency. In *irregular proliferation* (previously called "glandular hyperplasia", see LETTERER and MASSHOFF, 1941) the growth of the glands and stroma clearly exceeds that of the normal proliferative phase. The glands vary in their distribution, lying either closely packed or widely dispersed, and their diameters differ considerably. Some may be lined by a pseudostratified epithelium, others by a proliferated epithelium that forms several layers. The cellular stroma is composed of spindly cells and is irregularly edematous. Although the height of the endometrium varies considerably, it often can be extreme (Fig. 42b). Here, the cause of the anovulatory cycle is a persistent follicle that secretes excessive estrogen. We may regard the irregular proliferations as a direct precursor of glandular-cystic hyperplasia. It often is the first sign that estrogen levels are remaining elevated.

The *withdrawal bleeding* that sets in at the end of an anovulatory cycle must develop differently from a normal menstrual bleeding, since the fall of progesterone so necessary for a normal menstruation cannot take place. The withdrawal bleeding, therefore, represents bleeding due to cessation of estrogen secretion alone. Numerous theories have been postulated to explain how the bleeding is brought about. Initially the abnormal hormonal stimulation probably induces increased vascular fragility with changes in the ground substance and in the activities of enzymes and other substances (SCHMIDT-MATTHIESEN, 1965). Then as the levels of estrogen fall, additional circulatory disturbances are most likely provoked. With the loss of fluid the endometrium contracts, the vessels become compressed, and stasis follows, giving rise subsequently to thrombosis, hemorrhagic infarction and necrosis (MARKEE, 1950; CRAMER, 1952; HIN, 1957). Accordingly, dissolution of the reticulum fibers is not brought about by the action of relaxin and associated enzymatic proteolysis, as in a normal menstruation, but rather by necrosis. Hence, bleeding is often prolonged. At times when the estrogen decreases slowly the bleeding becomes unusually protracted. The regressive changes in the glandular and stromal cells, such as nuclear shrinkage and karyolysis, are more pronounced than in normal menstrual shedding (VASEK, 1947). Large fragments of tissue with intact reticulum fibers may be discharged (TERASAKI, 1928) (Fig. 43).

On the other hand, if the bleeding after an anovulatory cycle is of short duration, then it probably was not proceeded by a persistent follicle. Instead, we may assume that the endometrium is inadequately developed and involuting, chiefly by shrinkage as in hypomenorrhea.

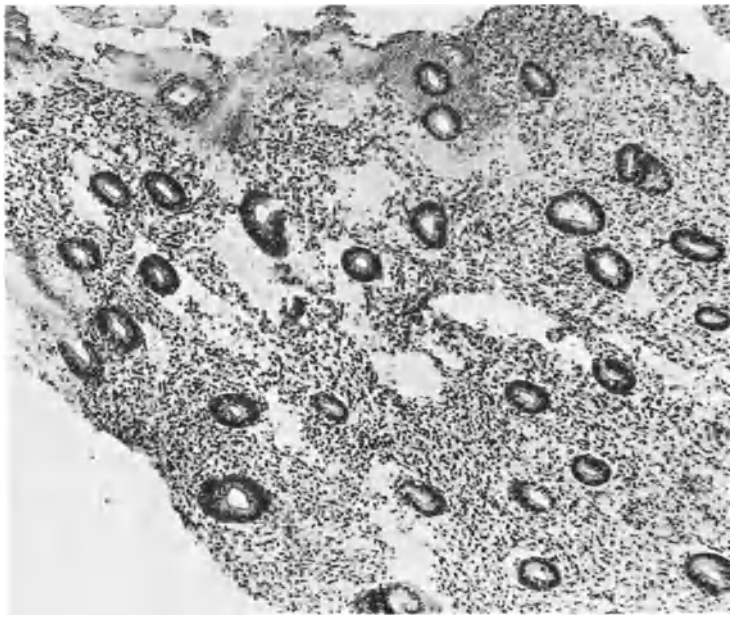


Fig. 43. Withdrawal bleeding in the fourth week of an anovulatory cycle

β) **Glandular-Cystic Hyperplasia** of the endometrium usually is the morphological consequence of either: 1) a persistent follicle that has maintained high levels of estrogen over a long period (SCHRÖDER, 1915), or 2) repeated anovulatory cycles with limited persistence of follicles, as in polycystic ovarian disease, or 3) repeated follicular atresia with hyperplasia of estrogen-secreting theca cells. Occasionally, 4) the recurrent development of severe luteal insufficiency may also result in endometrial hyperplasia. Other causes for the hyperplasia may be exogenous sources (prolonged therapy with estrogens; FROMM, 1959) or endogenous pathological conditions that produce excessive estrogen, such as stromal hyperplasia (NOVAK *et al.,* 1965; BILDE, 1967) or reactive forms found about ovarian tumors, which themselves secrete no estrogens (MACDONALD *et al.,* 1976), hilar-cell hyperplasia (HUSSLEIN, 1948; DHOM, 1952), thecomas and granulosa-cell tumors (LIMBURG, 1947; FIENBERG, 1958; KOTTMEIER, 1959). Here the height of the estrogen is less important than the duration of its unopposed (by gestagens) effect. Glandular-cystic hyperplasia is most common between the ages of 41–50 years, a period when ovarian function is in transition, as evidenced by pronounced fluctuation in estrogen production (GRUNER, 1942; SCHRÖDER, 1954). The condition is comparatively rare in adolescent girls (FRASER and BAIRD, 1972). It has been known for many years that glandular-cystic hyperplasia can be produced in animals by excessive estrogen (for review of literature see TAYLOR, 1938; MEISSNER *et al.,* 1957), in organ cultures of human endometrium when estradiol is added to the medium (DEMERS *et al.,* 1970), and in women by immoderate therapy with estrogen (SCHRÖDER, 1954; BLOOMFIELD, 1957). FASSKE *et al.* (1965) have confirmed these observations with elec-

tron-microscopic studies. Depending on the duration and constancy of the hyperestrogenism and on the individual sensitivity to the hormone, the endometrium responds by various changes, all of which may be seen in glandular-cystic hyperplasia. The most common is the *homologous hyperplasia,* in which the glands and stroma proliferate concurrently (LETTERER, 1948) (in about 65 per cent of the cases of STOLL, 1949). The *heterologous hyperplasia* may be subdivided into the *interstitial* type, in which the stromal proliferation predominates (in about 25 per cent of STOLL's cases, 1949) and into the *glandular* type, in which hyperplasia of the glands prevails (in about 10 per cent of the cases) (Table 7). Perhaps the kind of estrogen compound that stimulates the endometrium is also important in regulating the type of changes produced. Estradiol induces generalized proliferation of the glands. Estriol, however, is thought to cause primarily a proliferation of the basalis (PUCK *et al.,* 1957).

Grossly the endometrium is almost always tall, varying from 3–12 mm in height and in extreme cases may measure up to 20 mm. Its surface may be either smooth or irregular with polyps. The surface of these polyps is shiny and sleek, in contrast to that of a papillary carcinoma. In general, the hyperplastic endometrium is edematous and glassy. Occasionally some of the greatly dilated, cystic glands can be seen with the naked eye (Fig. 44).

Histologically, it becomes impossible to distinguish the three layers of the endometrium; they are obliterated by the marked proliferative changes. In the homologous type of glandular-cystic hyperplasia the intense mitotic activity of the glandular and stromal cells leads to an expansion in the volume of the stroma and an extension in the surface-area of the glands. This increase in the glandular epithelium comes about in three ways (LETTERER and MASSHOFF, 1941): by cystic dilatation, which is most common, by an abnormal enhancement of glandular tortuosity, and by the protrusion of epithelial papillae into the lumen. In the most common type of glandular-cystic hyperplasia the glands, although not increased in number, proliferate intensely and undergo cystic dilatation, producing in the endometrium the characteristic "Swiss-cheese" appearance (Fig. 45). In reconstructions of serial sections it could be shown, that in addition

Table 7. The hyperplasias of the endometrium

Homologous forms:	
glandular-cystic hyperplasia (active form)	→ adenomatous hyperplasia leading eventually to carcinoma → resting form → regressive hyperplasia
focal hyperplasia hyperplasia of the basalis polypoid hyperplasia	
Heterologous forms:	
stromal hyperplasia	→ leading eventually to endometrial sarcoma → regression
glandular hyperplasia (transitional endometrium of the climacterium)	

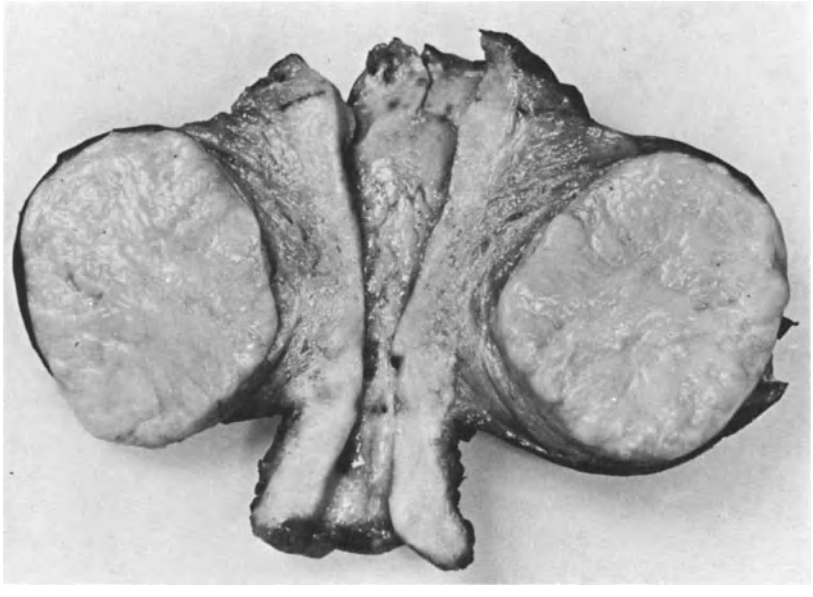


Fig. 44. Uterus from total hysterectomy, laid open to show hyperplastic endometrium and an intramural leiomyoma

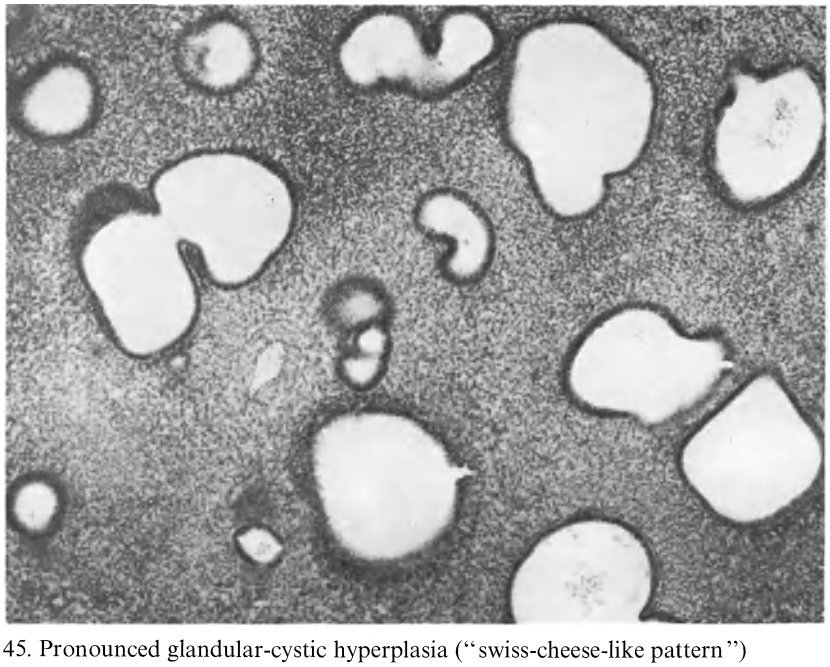


Fig. 45. Pronounced glandular-cystic hyperplasia ("swiss-cheese-like pattern")

to the intense proliferation of the glandular epithelium, the cystic dilatation is due to a constriction of the gland in the narrow neck-part near the surface (RATZENHOFER and SCHMID, 1954) caused by pressure from the growing stroma or by unequal epithelial proliferation.

The luminal margin of the *glandular epithelial cells* is sharp, as is that of the superficial epithelium. The cells are uniformly tall and, depending on the degree of hyperplasia, may be pseudostratified (Figs. 46 and 47). Their nuclei are elongated, the chromatin dense; their cytoplasm, although sparse, contains abundant RNA; consequently it stains blue. Several large nucleoli with dense ultrastructures may be seen in the nuclei. Many of the cells may be undergoing mitosis. Not only are the mitoses increased in number but are often blocked in prophase or metaphase by the excessive estrogenic stimulation (PICARD, 1949). Such a disturbance of mitosis could explain the frequent occurrence of "clear cells" in the glandular epithelium, which FUCHS (1959) held as forerunners of mitosis. SARBACH (1955) found many "swollen cells" in the hyperplastic glandular epithelium and regarded them as pathological mitoses that had failed to reach completion. The synthesis of DNA in the epithelium in the actively proliferating and less cystically dilated glands is greatly intensified (FETTIG, 1965). As measurements have proven, the nuclei are enlarged (PICARD, 1950). The more the glandular epithelial cells proliferate, the greater their content of RNA becomes (ATKINSON *et al.*, 1949; REMOTTI, 1956; MOOKERJEA, 1961). In the extremely dilated, cystic glands the RNA may decrease again (BREMER *et al.*, 1951). Droplets of glycogen can always be demonstrated (ATKINSON *et al.*, 1952; CRAMER and KLÖSS, 1955; BUSANNI-CASPARI and UNDEUTSCH, 1956; RUNGE *et al.*, 1956; ARRONET and LATOUR, 1957; LEWIN, 1961; STRAUSS, 1963). The number of small droplets

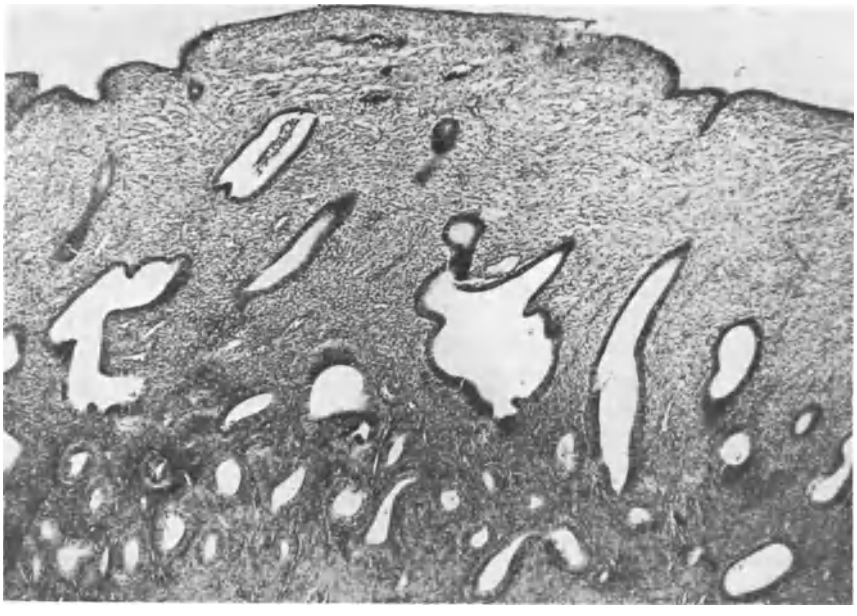


Fig. 46. Beginning glandular-cystic hyperplasia

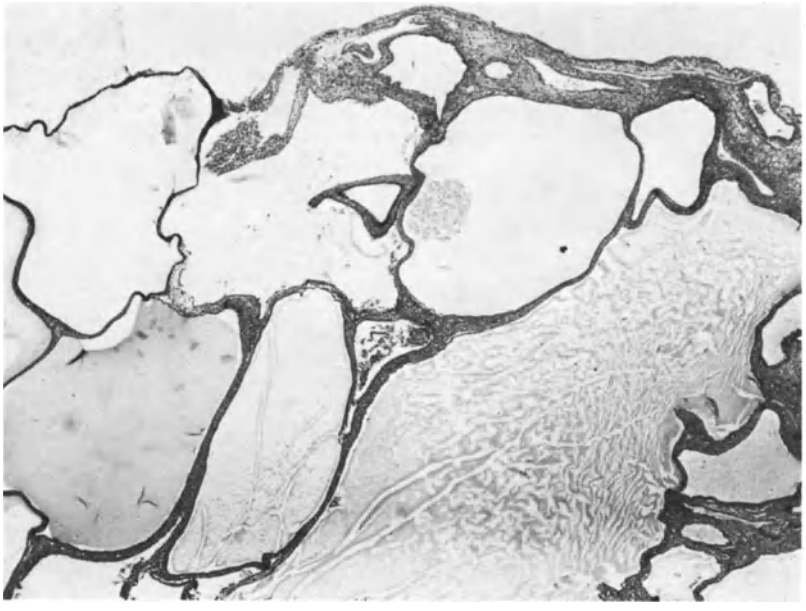


Fig. 47. Extreme glandular-cystic hyperplasia with almost complete loss of the stroma between the greatly dilated cysts lined by flattened epithelial cells

found is comparable to that of the mid proliferative phase (FASSKE *et al.*, 1965). Granules of lipid are increased (CRAIG and DANZIGER, 1965). The glands contain more mucus than normal (SALM, 1962); especially the acid mucoids accumulate at the apical margin of the cell. The increase in the activity of alkaline phosphatase is directly proportional to the level of estrogen (ATKINSON and GUSBERG, 1948; HALL, 1950; MCKAY *et al.*, 1956; LEWIN, 1961; MOOKERJEA, 1961; KUCERA, 1964; FILIPPE and DAWSON, 1968). The activity of acid phosphatase and esterase are decreased (GOLDBERG and JONES, 1956; MCKAY *et al.*, 1956). HUGHES (1976) suggests that faulty hormonal control of endometrial metabolism may lead to the increased activities of TPN-isocitric dehydrogenase and glucose-6-phosphate dehydrogenase found in hyperplastic and cancerous endometria. He postulates the increased activities of these enzymes may be the basis for further altered cellular metabolism and ultimate transformation to uncontrolled cell growth.

Electron-microscopically, several types of glandular cells may be distinguished in glandular-cystic hyperplasia (WESSEL, 1961). The first type resembles the epithelial cell of the proliferative phase but has shorter microvilli and its cytoplasm contains numerous granules of lipid and a widely distributed Golgi apparatus. The second type of cell is dark with cytoplasmic processes, numerous ribosomes, osmiophilic granules and a nucleus rich in DNA. The third type is the clear cell, some of which are ciliated (HAMPERL, 1950); others represent degenerating cells after interrupted mitoses (SARBACH, 1955; FUCHS, 1959).

In the *stroma* the characteristic signs of differentiation induced by progesterone fail to develop. The stroma consists of cells with scanty cytoplasm and no glycogen.

Many of the nuclei are small, rich in chromatin and densely spaced. Others, however, are large, have little chromatin, are widely dispersed, and show minimal proliferative activity (FETTIG, 1965). Granulocytes are not evident. Mast cells may be abundant (RUNGE *et al.*, 1956). Although the reticulum fibers become increased in number and thickness (WERMBTER, 1924; TIETZE, 1934; CENTARO and SERRA, 1949; ECKERT, 1955) their distribution varies, and in many places they are pulled apart by focal edema. Typical collagen fibers are lacking (in contrast to atrophic endometrium). The ground substance varies as well. Where the stroma is dense it contains abundant mucopolysaccharides and protein. In the edematous regions the stroma is partly depolymerized and often contains fibrin-like exudates, apparently the result of increased vascular permeability (SCHMIDT-MATTHIESEN, 1965). The fibrinolytic activity is high. The spiral arteries and arterioles are poorly developed and run a straight course (SCHRÖDER, 1954; BEILBY *et al.*, 1971); that is, since progesterone is necessary for their proliferation, none takes place, hence the vessels merely suffice to nourish the tissue (MASSHOFF and KRAUS, 1955). In contrast, the superficial capillaries and venules are very numerous, dilated and often congested. Some may contain hyaline thrombi that occlude part or all of the vessel lumen (Fig. 48a). One may find many similar hyaline deposits lying in the stroma; most probably these represent thrombi extruded from ruptured vessels (MASSHOFF, 1941). Eventually these hyaline deposits become organized. In addition, there are often localized fresh and old hemorrhages in which focal hemorrhagic necroses may develop (Fig. 48b).

Like the bleeding at the end of an anovulatory cycle, the shedding of a glandular-cystic hyperplasia is clinically characterized by a protracted bleeding after a long interval; that is, after about three months—the time required for a relative deficiency of estrogen to develop. It also represents a pathological *withdrawal bleeding* caused by estrogen deficit. The deficiency may be brought about in various ways: 1) Under constantly rising levels of estrogen the endometrium grows higher and higher until one day the concentration of estrogen becomes insufficient to sustain the voluminous tissue. By means of this relative estrogen deficiency the endometrial tissue then degenerates ("breakthrough bleeding"), although the level of estrogen in the blood remains stable (LETTERER, 1948). 2) Through feedback mechanisms the level of estrogen may be depressed by the pituitary, perhaps even quite early; the decrease in estrogen will however lead to the same effect of breakthrough bleeding. As in the anovulatory cycle, the relative or absolute decrease of estrogen is only the last factor in a long sequence that induces the breakthrough bleeding. The protracted bleeding from the non-dissociated mucosa (for dissociated mucosa, see menstruation, p. 73) comes about in the following manner. Owing to the abnormally developed vascular bed and the aberrant composition of the stroma and ground substance, the circulation in the endometrium becomes slowed and inadequate. Thrombi form. The vessels soon rupture, hemorrhage occurs, deposits of hyaline thrombotic material are extruded into the stroma, and necroses develop. Shedding often proceeds with a brisk and unremitting menorrhagia, not only because the lack of relaxin prevents the mucosa from disintegrating but also because the further secretion of estrogen stimulates the remaining mucosa to proliferate. In addition, proteolytic enzymes become activated that inhibit coagulation in the endometrium

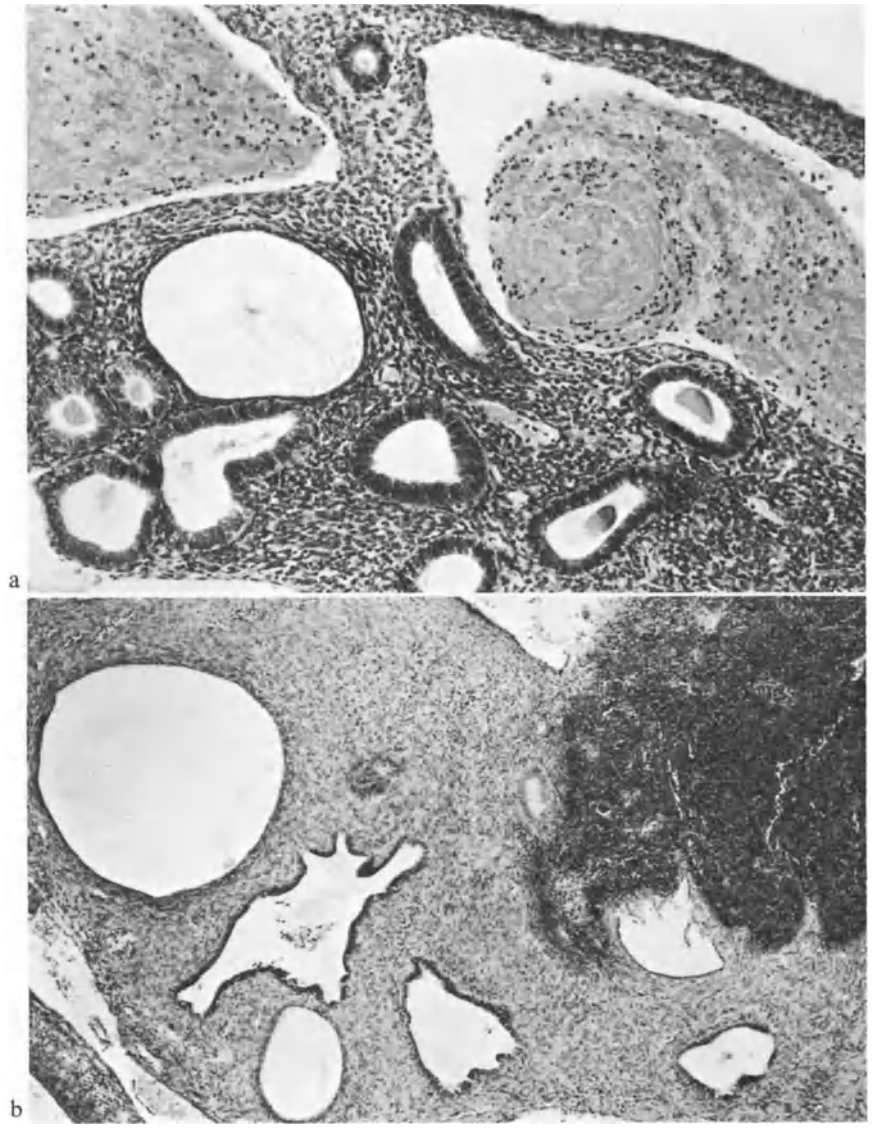


Fig. 48a and b. Hyaline thrombi (a) and focal hemorrhagic necroses (b) in a glandular-cystic hyperplasia

while it is slowly shed. On the other hand, estrogen causes the fibrinolytic activity to rise (SCHMIDT-MATTHIESEN, 1965, 1967). Perhaps the many hyaline (fibrinoid) deposits so characteristic of glandular-cystic hyperplasia represent products of partial fibrinolysis that, for reasons of local deficiencies in enzyme activities, are left behind in the tissue to organize.

After a prolonged menorrhagia the major part of the hyperplastic endometrium may eventually be discharged. A curettage carried out at this time yields

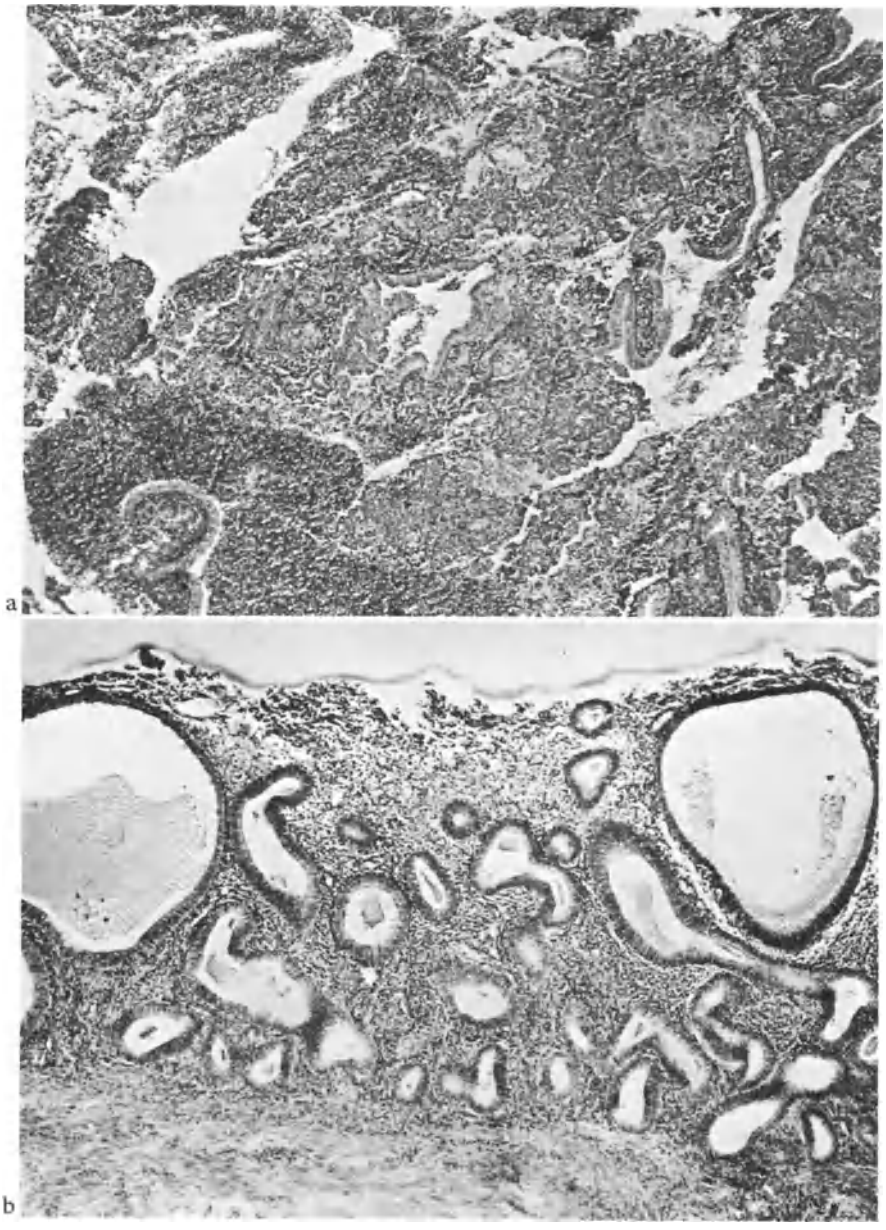


Fig. 49 a and b. Remnants of a partially discharged hemorrhagic glandular-cystic hyperplasia. (a) Remnants obtained by curettage after several weeks of bleeding; cysts collapsed and the stroma shows complete hemorrhagic necrosis. (b) Cystically dilated glands remaining in the basalis of an extirpated uterus

only sparse, hemorrhagic remnants with shrunken stroma and collapsed glands, whose circumferences perhaps suggest they had originally been cystic (Fig. 49). Our diagnosis in such instances is *discharged glandular-cystic hyperplasia*. In

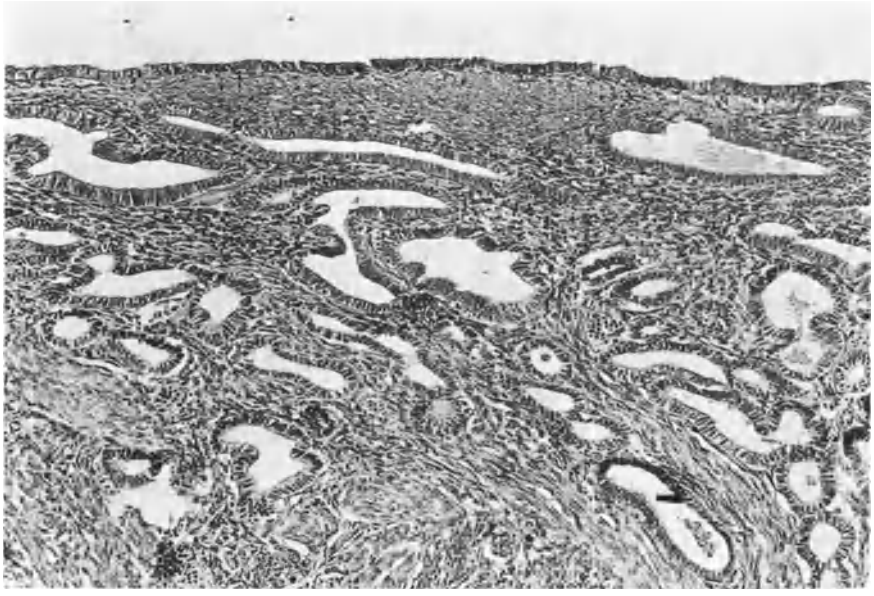


Fig. 50. Glandular-cystic hyperplasia developing again at site where it was previously shed

extreme cases when almost all endometrial tissue has been shed, that diagnosis cannot be made histologically. Since glandular-cystic hyperplasia tends to recur (Fig. 50) (according to TIETZE, 1934, in 67.2 per cent of young women and in 36.3 per cent of older women) a repeat curettage after a long interval and at the onset of a renewed, extended bleeding usually leads to the diagnosis.

Secretory changes occasionally occur in a glandular-cystic hyperplasia without hormonal treatment (according to GRUNER, 1942, in 6.2 per cent; according to BEHRENS, 1954, in 3 per cent of the cases). Glycogen may accumulate in some epithelial cells as solitary basal vacuoles. We surmise these accumulations are stimulated by small amounts of progesterone secreted either by the ripe follicle, as at the end of the proliferative phase, or by the temporarily luteinized cells in the persisting follicle (BUSANNI-CASPARI and UNDEUTSCH, 1956; HINZ, 1957). At times even sporadic stromal cells differentiate. Further spontaneous (unprovoked) changes of differentiation however are rare. In contrast, with progestational therapy or with clomiphene the cystically dilated glands may undergo secretory change (Fig. 51) and the fibrinolytic activity of the stroma may disappear. Depending upon the type of gestagen administered, predecidual or decidual changes may also develop (KISTNER *et al.*, 1966). Occasionally such therapy induces the endometrium to regress to a normal state or even to atrophy (WENTZ, 1966).

Small nodules of *squamous epithelium* sometimes arise from the glandular epithelium of the hyperplastic endometrium (HUNZIKER, 1911; according to KUTLIK, 1962, in 2.5 per cent of all endometria examined). Most probably these nodules represent squamous metaplasia of columnar epithelial cells, or perhaps of pluripotential cells of the Müllerian epithelium (MEYER, 1922; HINTZE, 1928;

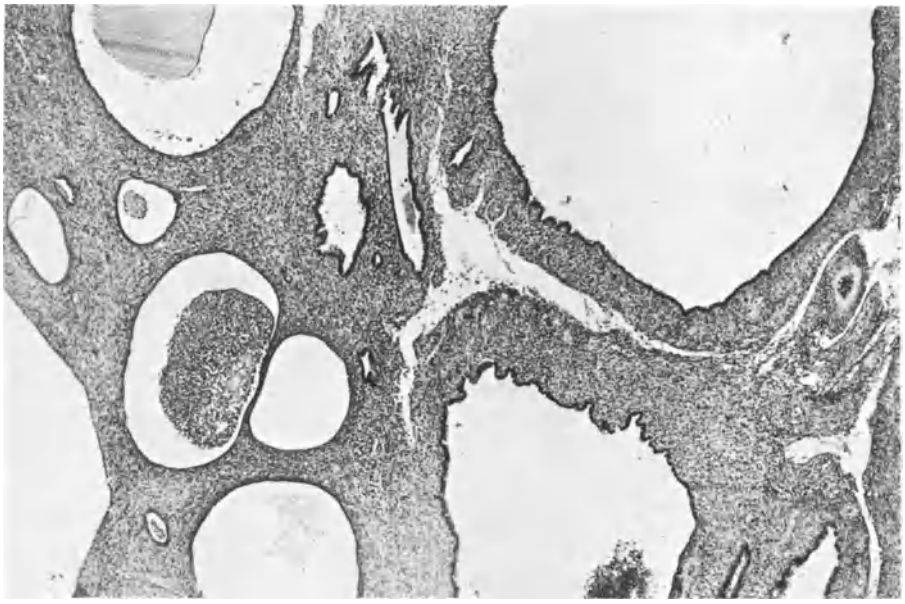


Fig. 51. Secretory transformation of some of the glands of a glandular-cystic hyperplasia

FLUHMANN, 1928, 1953, 1954; BRUNTSCH, 1950). The assumption of STRAUSS and HIERSCHE (1963) that these nodules arise from "dedifferentiated descendants of the endometrial epithelium" seems less plausible. The cells making up the nodules have histological characteristics that are typical of squamous epithelium. They may cornify centrally as the phloxine-tartrazine stain clearly shows. A basement membrane can often be made out delimiting the nodules from the surrounding stroma (see Fig. 52). Merely because the cells lack intercellular bridges does not mean they are not of squamous epithelial origin. Frequently the nodules protrude into the glandular lumen and may even fill it. At other times they grow outwards, bulging into the stroma. We regard the appearance of the nodules of squamous epithelium merely as an individual variation in the reaction of the endometrium to elevated levels of estrogen. Among other observations supporting our view is the longterm prospective follow-up of patients who were observed to pass through all stages of hyperplasia, ending with a carcinoma. As these observations disclosed, if nodules of squamous epithelium were demonstrable in the glandular-cystic hyperplasia then they were also found in the subsequent adenomatous hyperplasia, and the carcinoma ultimately developing from that proved to be an adenoacanthoma since it also contained nodules of squamous epithelium. The appearance of the squamous epithelium in the glandular-cystic hyperplasia, however, in no way predisposes to the development of a carcinoma. The nodules in the adenoacanthoma usually represent remnants of metaplastic squamous epithelium that arose in the pre-existing benign hyperplasia. They commonly appear after years of estrogen therapy (see Fig. 53; cf. SIEGERT, 1938; GOSCH, 1949). Similar changes have been produced in animals with estrogen (GUMBRECHT, 1936).

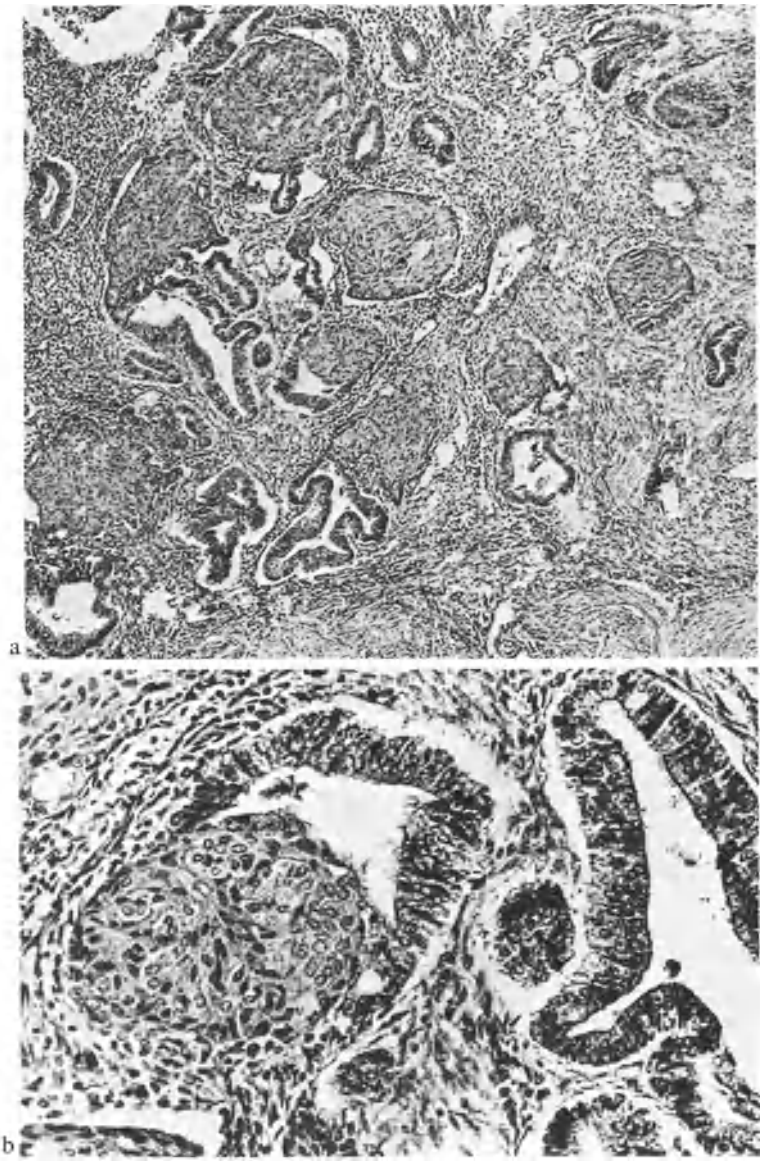


Fig. 52a and b. Nests of squamous epithelial cells in glandular epithelium of a glandular-cystic hyperplasia. (a) Low magnification. (b) Higher magnification

The duration of the hyperestrogenism determines what happens to the glandular-cystic hyperplasia. If the levels of estrogen fall with the onset of menopause, then regressive changes may appear. If the hyperestrogenism persists, either because of abnormal endogenous production or because of continued therapy with estrogen, then glandular-cystic hyperplasia progresses to an adenomatous hyperplasia (see Table 4). Whereas glandular-cystic hyperplasia develops most com-

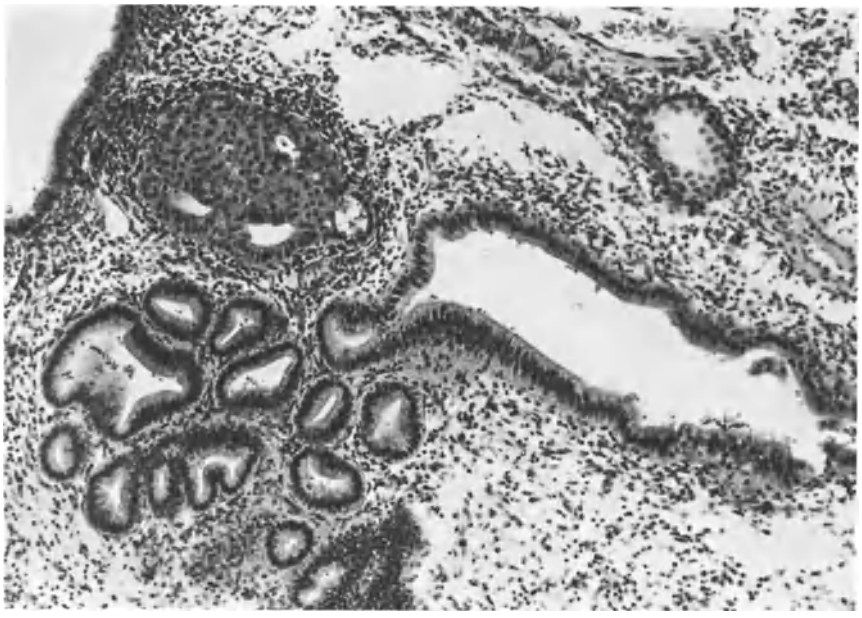


Fig. 53. Glandular-cystic hyperplasia with squamous metaplasia and beginning adenomatous proliferation after years of estrogen therapy during the postmenopause

monly at the beginning and end of the reproductive years because these periods of adaptation predispose to anovulation and persistent follicles, after the menopause the histological picture of hyperplasia changes.

As ovarian function wanes, the secretion of estrogen gradually subsides, finally falling to such levels that endometrial proliferation ceases and no withdrawal bleeding occurs. Mitoses become rare; the glandular epithelial cells become more cuboidal. This histological picture of *resting glandular-cystic hyperplasia,* although fully developed in all other respects, can still be distinguished from the *active* form (KAISER and SCHNEIDER, 1968). During subsequent years or decades, as atrophy increases, the resting form slowly transforms into *regressive hyperplasia* (Fig. 54). The glandular epithelium becomes a single row again, which flattens out more and more with time. The cells lose RNA and cytoplasmic organelles, and their nuclei become rounded, small and hyperchromatic. The stromal cells shrink and become more closely packed. During this process of involution we have never observed the atypical proliferations of glandular cells that RATZENHOFER and SCHMID (1954) have described. We believe such atypical proliferations indicate rather an aberrant hormonal stimulation (see p. 235). The glands do not collapse but instead remain cystic well into old age. Thus we see a "petrified" state of the hyperplasia that had developed just before menopause set in when no withdrawal bleeding occurred because the estrogen levels had decreased so slowly. Regressive hyperplasia differs from the cystic, atrophic endometrium of the postmenopausal period (cf. p. 87; Fig. 35b) merely by its greater number of cystically dilated glands.

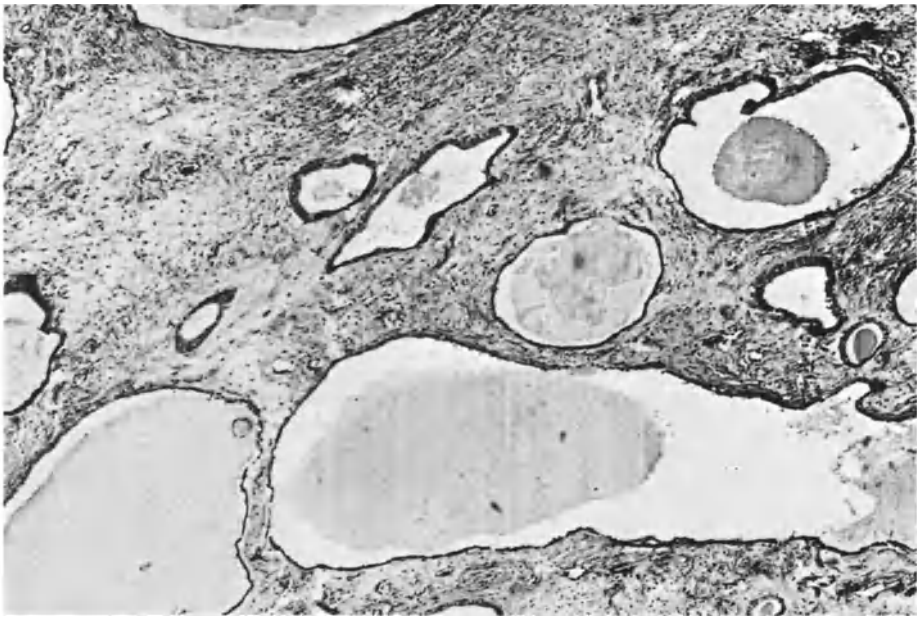


Fig. 54. Regressive hyperplasia with flat, in part endothelial-like glandular epithelium and stroma poor in cells

If the secretion of progesterone ceases at menopause but that of estrogen continues at high or moderately high levels then we speak of an unopposed estrogenism. That stimulates the glandular-cystic hyperplasia to further sustained growth, leading to the development of an **adenomatous hyperplasia.** The proliferation, until now principally characterized by cystically dilated glands, sharply accelerates. The glandular epithelium begins to bud, sending forth offshoots; the *new glands* that form are in part quite small and of the branched alveolar type (Figs. 55, 56). The larger glands are lined by tall columnar, stratified epithelium from which epithelial papillae develop to protrude into the lumen. The elongated, chromatin-rich nuclei of the epithelial cells begin to show abnormalities; their synthesis of DNA greatly increases (FETTIG, 1965). Their cytoplasm remains sparse but basophilic owing to abundant RNA. Cytoplasmic structures indicative of differentiation (progesterone effect) are absent. The histochemical reactions essentially resemble those of glandular-cystic hyperplasia (MCKAY *et al.*, 1956).

As the glands proliferate and grow they push the stroma lying between them together. It is gradually absorbed, so that ultimately the basement membranes of some of the glands come to touch one another (back-to-back position of the glands). In the remaining gusset-like patches of stroma groups of *foam cells* may be found in over 50 per cent of the adenomatous hyperplasias (Figs. 57, 58). They contain lipids that have a green autofluorescence. From histochemical reactions (DALLENBACH-HELLWEG, 1964) it seems these lipids are most probably either cholesterol esters, or estrogen derivatives. The foam cells show no relation-

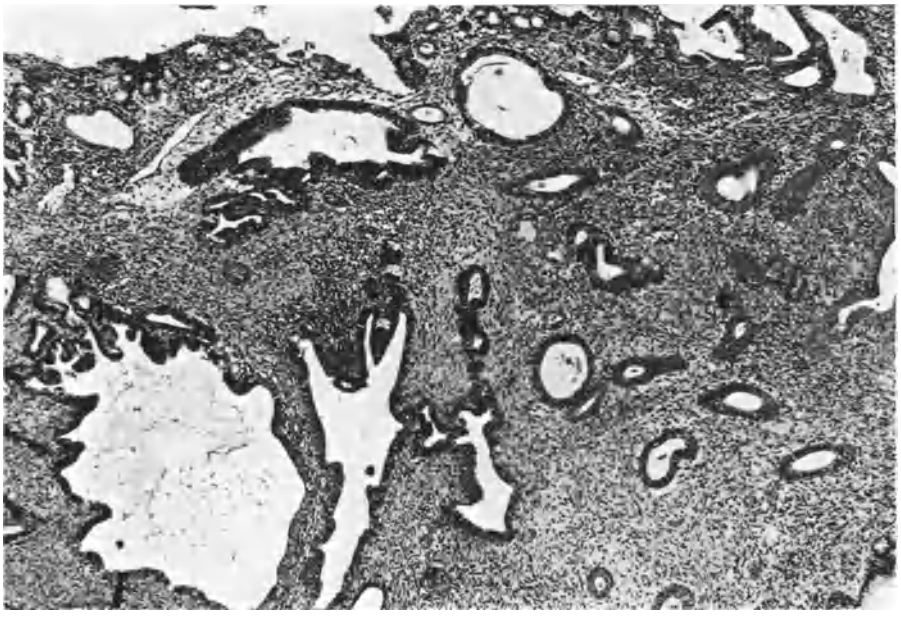


Fig. 55. Beginning adenomatous hyperplasia that has developed from a glandular-cystic hyperplasia by excessive epithelial proliferation, appearing here mainly as intraluminal (epithelial) papillae

ship to inflammatory processes, either etiologically or anatomically. They are, like decidual cells, transformed stromal cells and always associated with a hyperestrogenism, at times even with that resulting from estrogen therapy. They serve as reliable indicators that the levels of estrogen have remained elevated; they are especially useful in evaluating the prognosis of adenomatous hyperplasias. In general, the more numerous the foam cells the sooner an adenomatous hyperplasia progresses to a carcinoma. About 30 per cent of all glandular-cystic hyperplasias contain some foam cells in the stroma. It was in the stroma of such hyperplasias that first SCHILLER (1927) and later VON NUMERS and NIEMINEN (1961) discovered foam cells; SALM (1962) also found them in the stroma of polyps. The results of recent studies refute the notion that the endometrium is able to produce and secrete estrogenic substances (DALLENBACH and RUDOLPH, 1974). Perhaps a derivative of estrogen is stored in the cytoplasm of the foam cells, when the endometrial tissues are flooded by excessive estrogen they cannot properly metabolize. Cells morphologically identical to those in the endometrium appear in prostatic carcinomas after estrogen therapy (EPSTEIN, 1976).

Adenomatous hyperplasia develops under the influence of unopposed estrogen, consequently almost exclusively after the menopause. During the reproductive years it is seen only with persistent anovulation (as with the Stein-Leventhal syndrome), or following prolonged estrogen treatment (Fig. 58). Whether it regresses, remains, or progresses further depends on the secretion of estrogen. If the levels of estrogen fall or if gestagens are given as therapy, then adenomatous hyperplasia may regress. If the levels of estrogen remain elevated, however, as

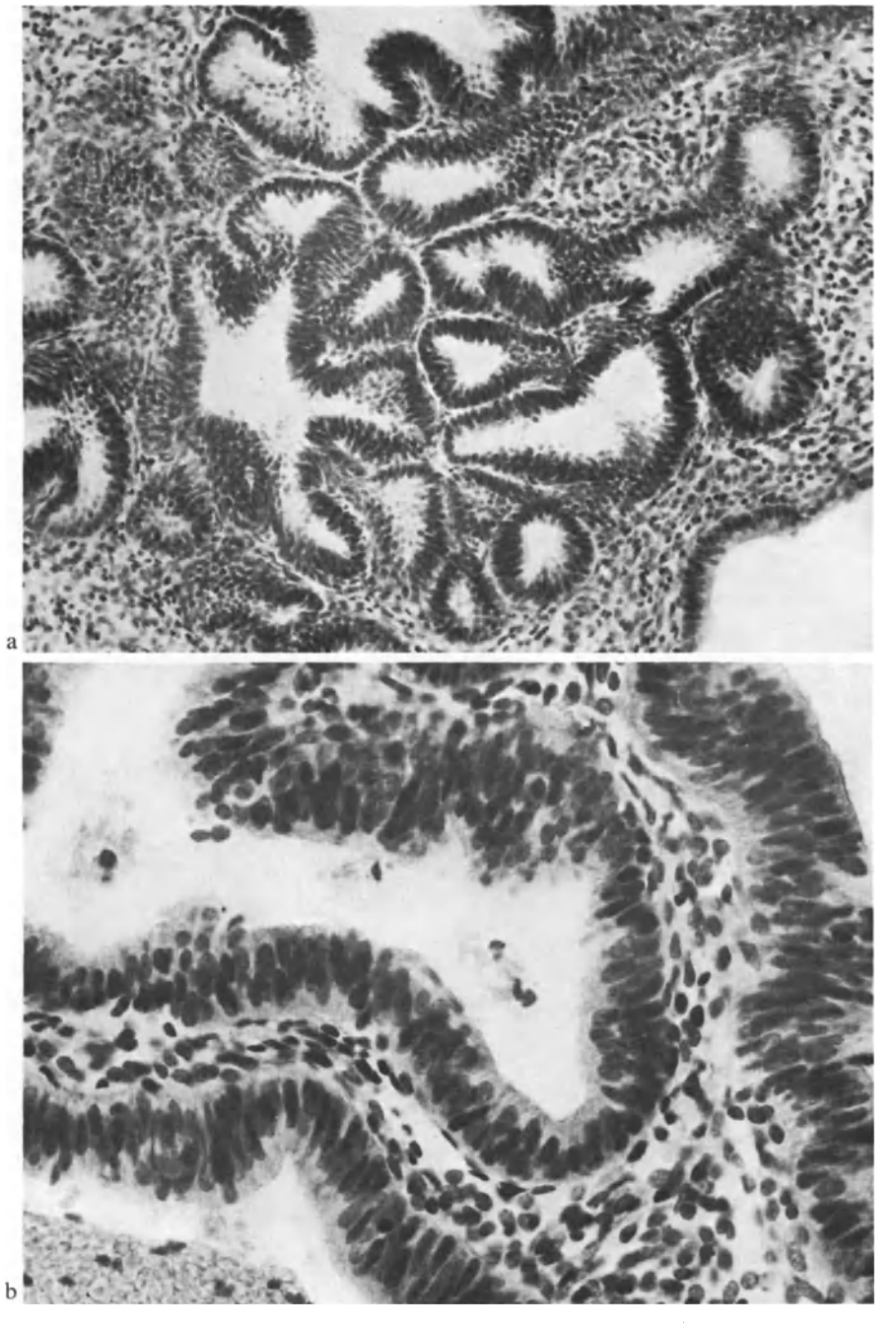


Fig. 56a and b. Adenomatous hyperplasia with extreme atrophy of the stroma and some alveolar branching of glands. The epithelium is pseudostratified or stratified. (a) Low magnification. (b) Higher magnification

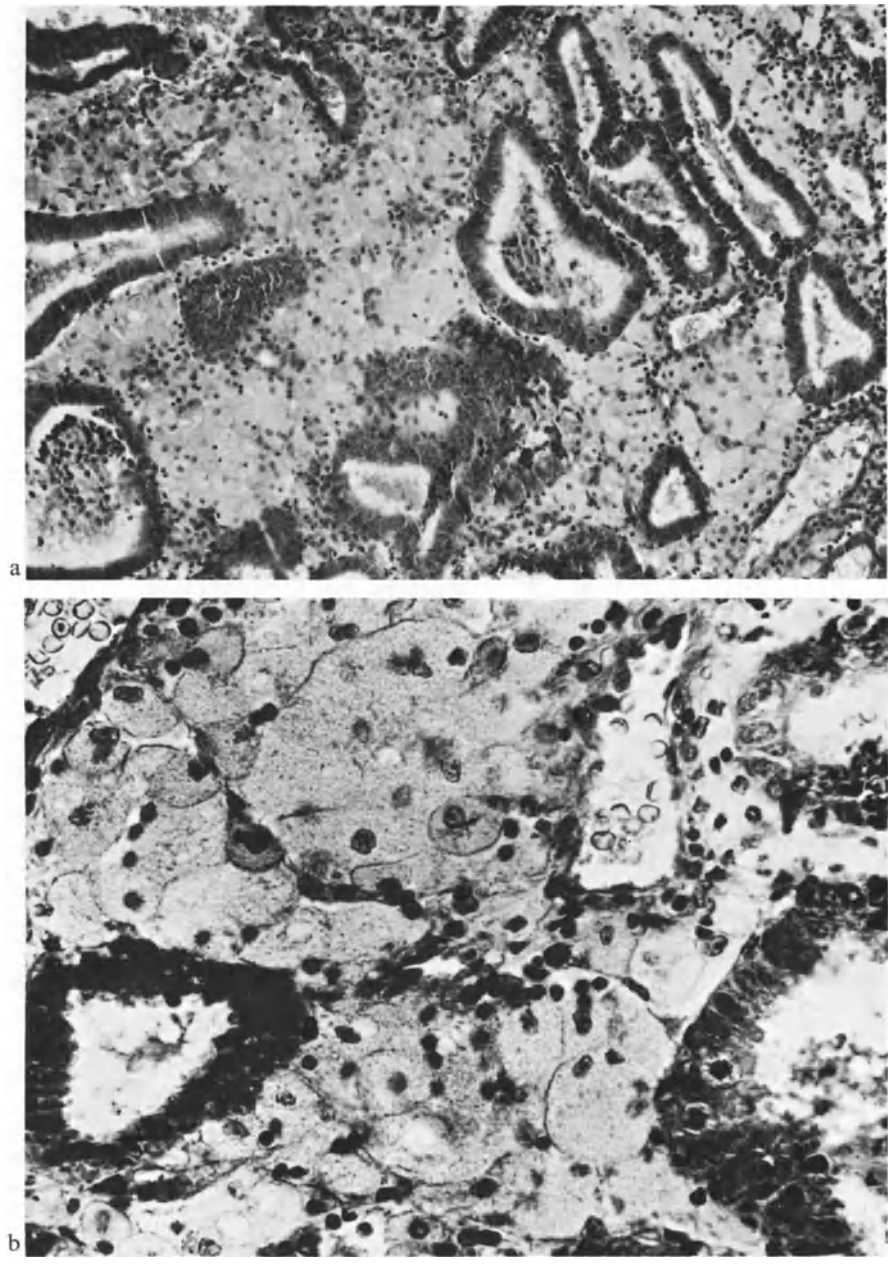


Fig. 57 a and b. Transformation of stromal cells into foam cells in adenomatous hyperplasia. (a) Low magnification. (b) Higher magnification

often they do after the menopause, then after various periods of time if the patient has a predisposing constitution the adenomatous hyperplasia through progressive overgrowth of its glands may develop into an adenocarcinoma (see p. 181; Fig. 60).

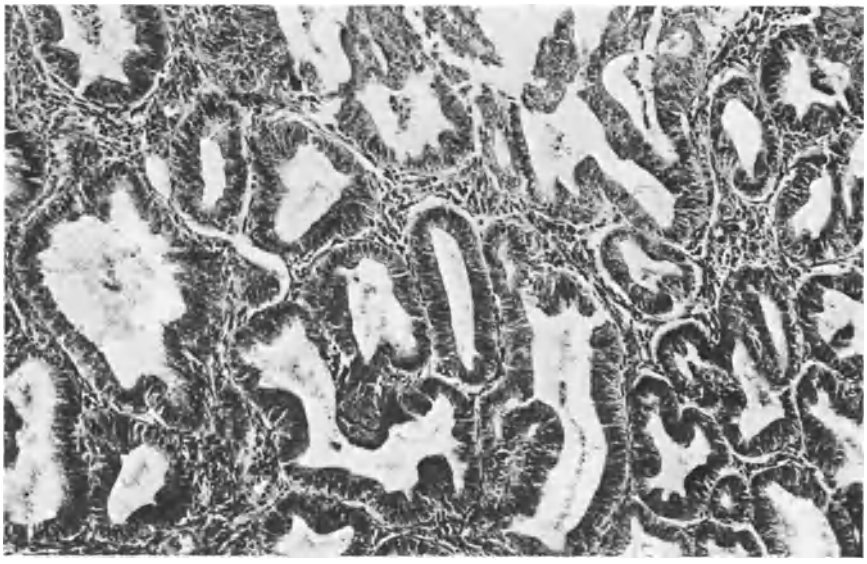


Fig. 58. Adenomatous hyperplasia of the endometrium that developed in a 37 year old woman after many years of estrogen therapy

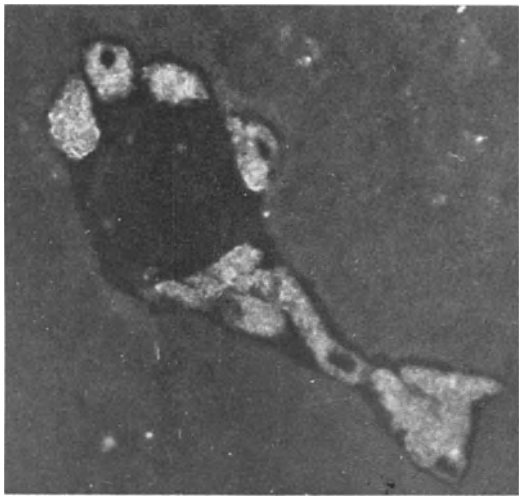


Fig. 59. Autofluorescence of foam cells

Early carcinomatous changes, as clusters of anaplastic glands, may occasionally develop in only one part of an adenomatous hyperplasia or also multicentrically (BUEHL *et al.*, 1964), but generally in the basalis. The cells of these carcinomatous glands are often distinct, for their cytoplasm is strikingly pale and clear because it contains only small amounts of RNA (MCKAY *et al.*, 1956). Their nuclei are large, round or polygonal and unevenly distributed (Figs. 61, 62). Cytophotometric studies of these nuclei reveal an aneuploidy like that found in invasive carcinoma; in contrast, the glandular-cystic hyperplasia and

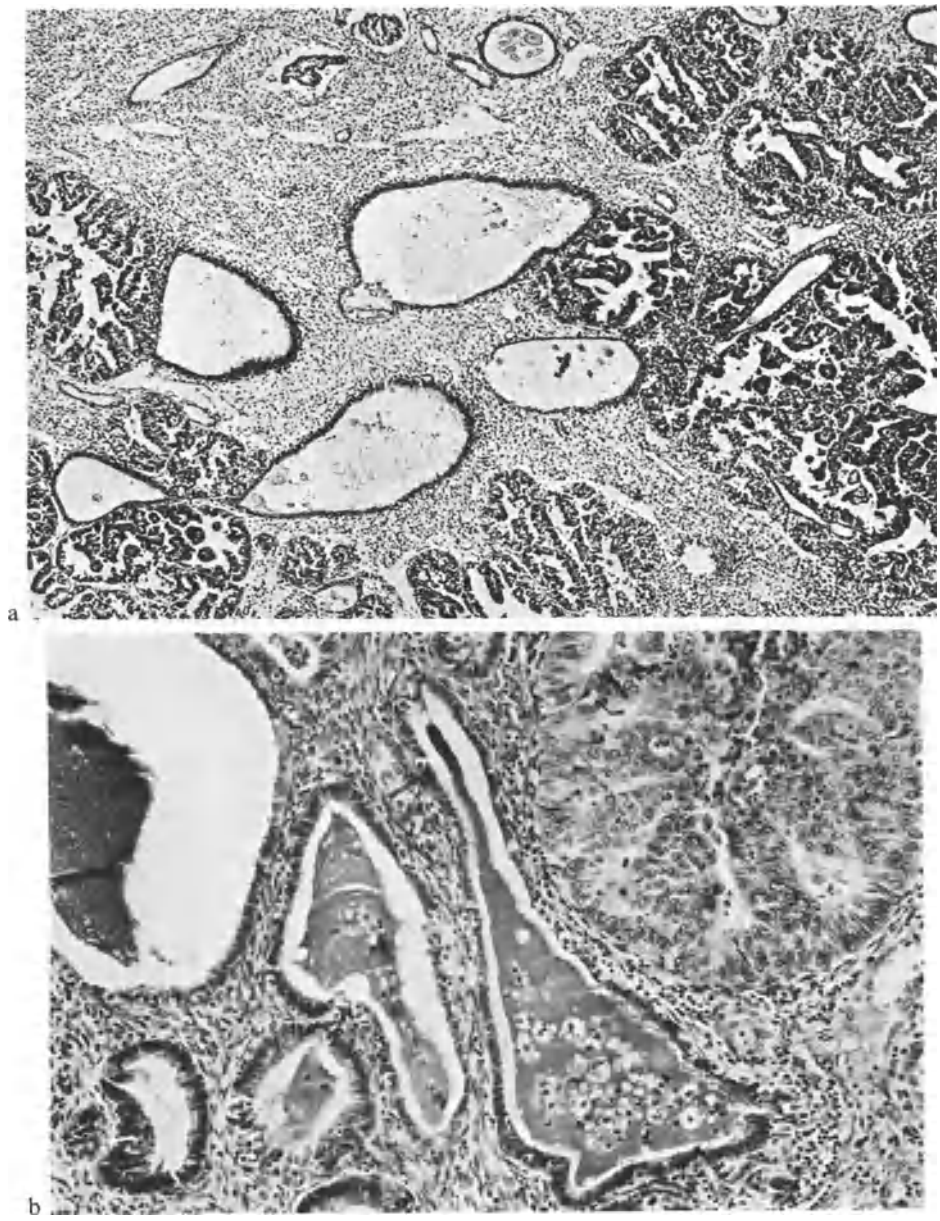


Fig. 60a and b. Adenomatous hyperplasia (a) and early adenocarcinoma (a and b) developing from a glandular-cystic hyperplasia

most of the adenomatous hyperplasias show unequivocal diploid values for DNA (WAGNER *et al.*, 1967). The chromatin is clumped, and the nucleoli are enlarged. Profound changes occur in the histochemical reactions but remain constant thereafter in the carcinoma. A good example is the switch in activity

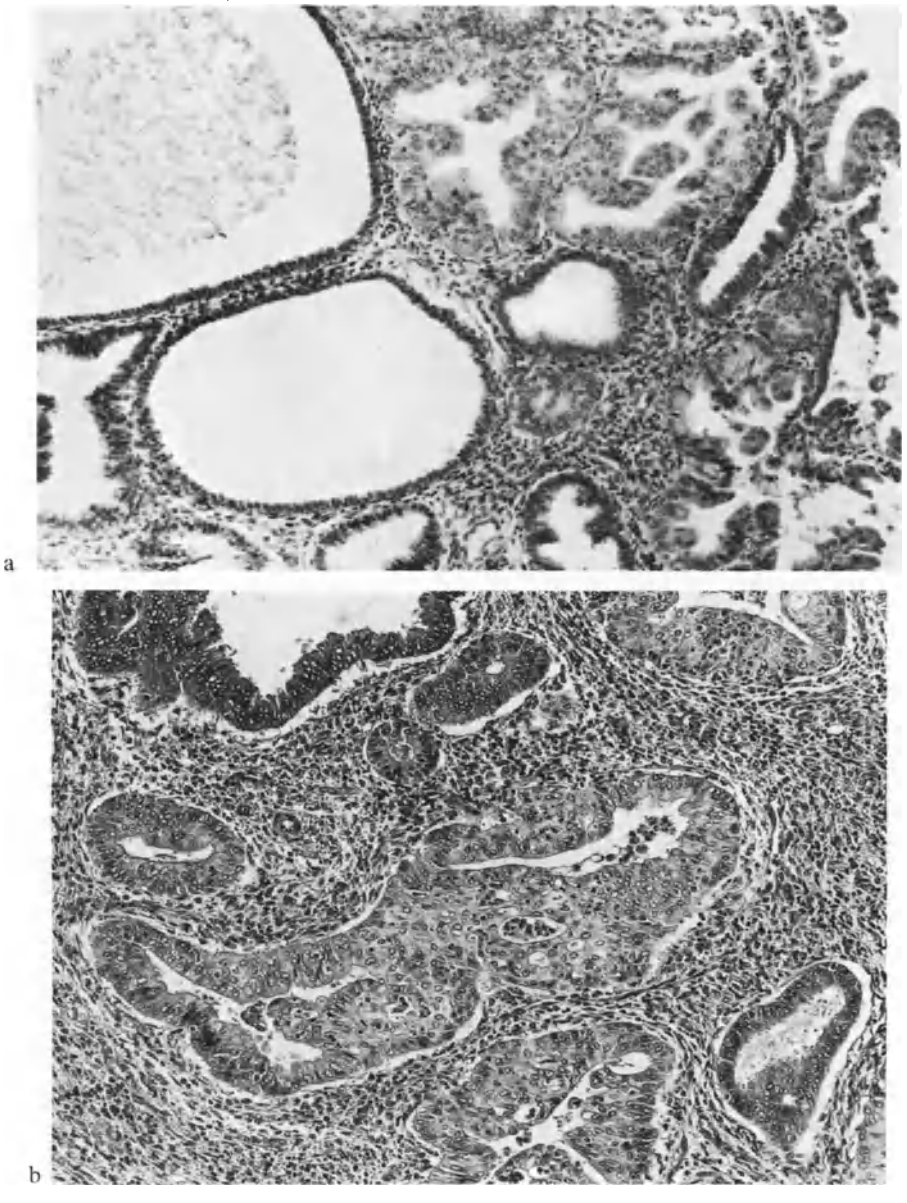


Fig. 61 a and b. Early adenocarcinoma with pellucid epithelial cells arising in an adenomatous hyperplasia

of the phosphatases during the transition: alkaline phosphatase decreases, whereas acid phosphatase rises. Because it resembles a secretory endometrium, early carcinoma often goes unrecognized, or it may mislead one into believing that an adenomatous hyperplasia is undergoing secretory changes. The PAS stain readily decides the issue: the glands of the early carcinoma are free from glyco-

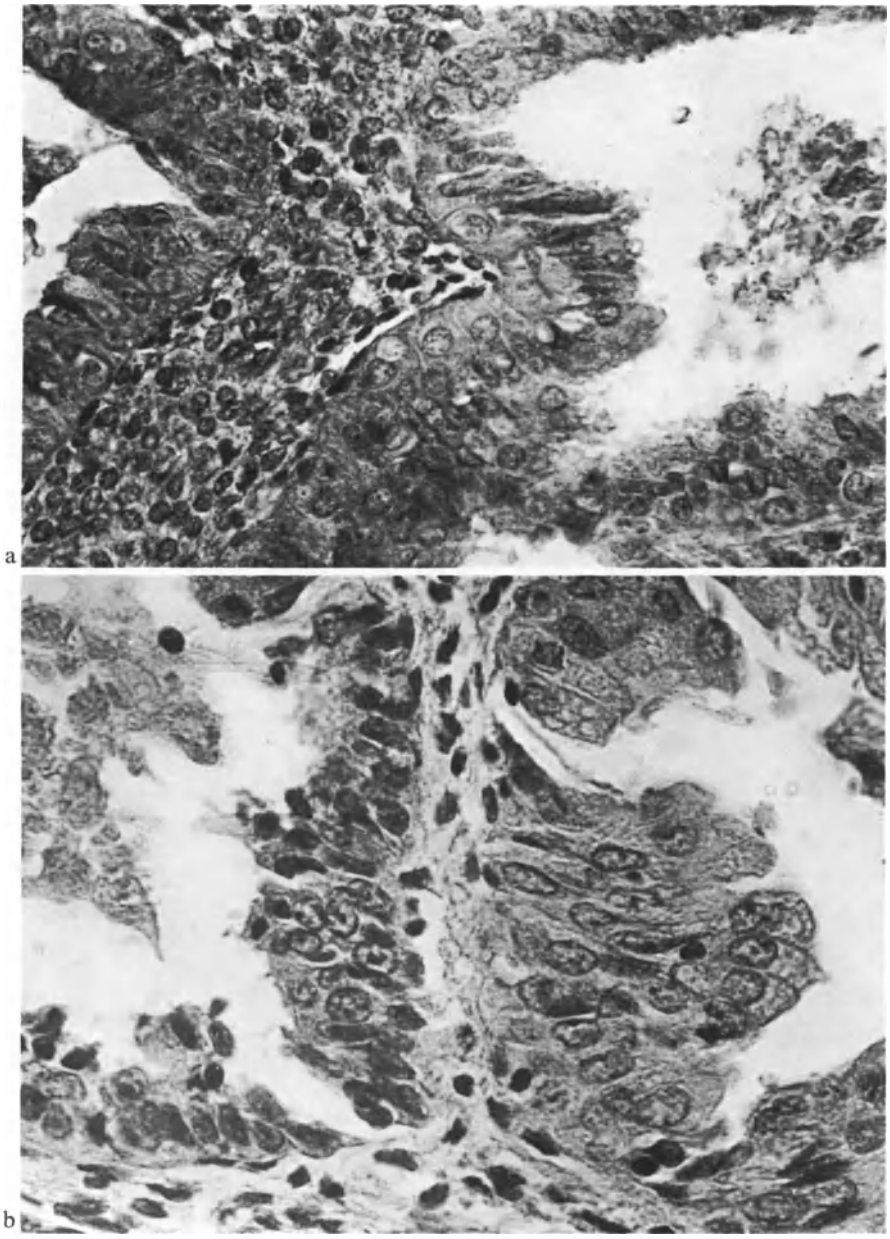


Fig. 62a and b. Tubular structure of an early adenocarcinoma (at the right) next to adenomatous structures (at the left). (a) Basally located round nuclei push away the overlying elongated nuclei of the adenomatous hyperplasia. (b) The nuclei of the early adenocarcinoma are aneuploid

gen. The focal excessive proliferation associated with the adenomatous hyperplasia paves the way, so to speak, for the transformation into carcinoma. The change is like that occurring in a carcinoma in situ of the cervix which causes

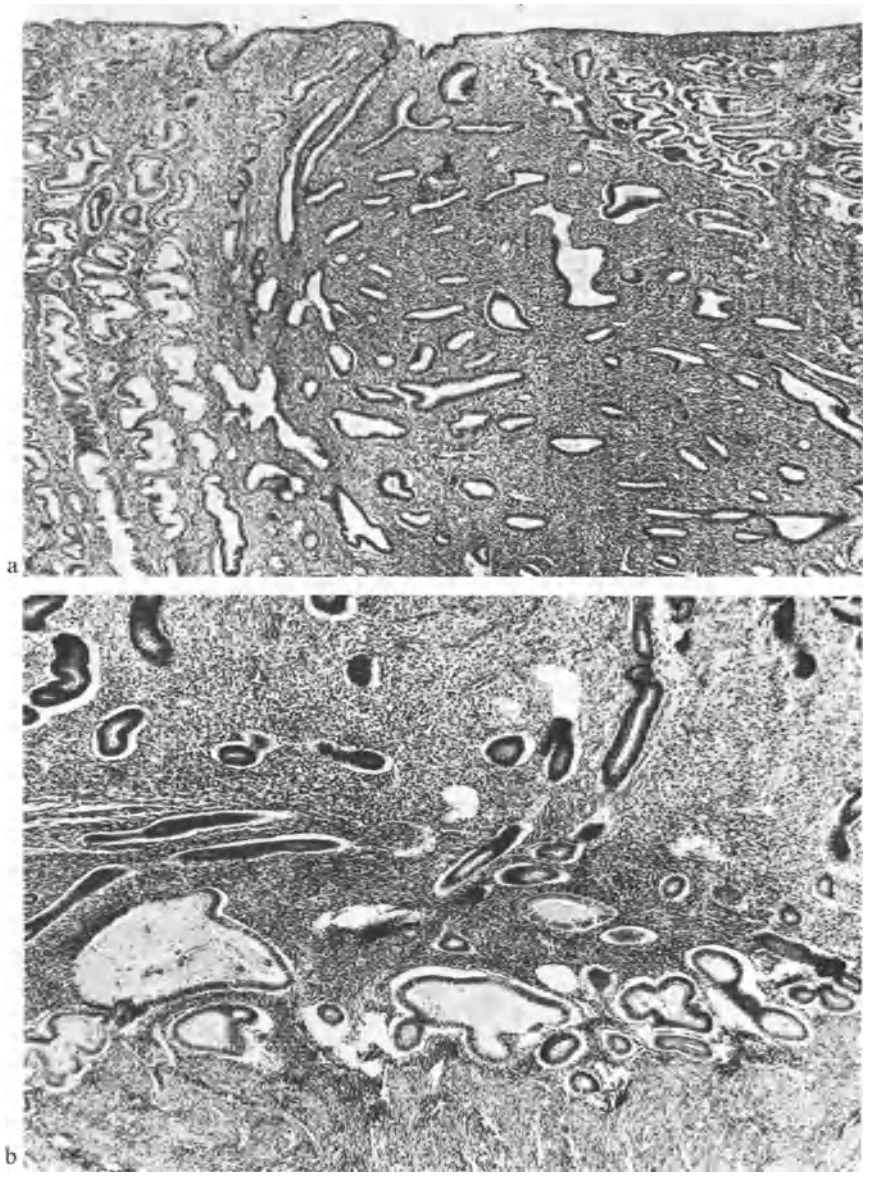


Fig. 63. (a) Focal hyperplasia, pushing normal secretory glands aside. (b) Hyperplasia of the basalis. Basal glands cystically enlarged; the glands of the functionalis are proliferating normally

it to invade. CULLEN (1900), R. MEYER (1923) and LAHM (1928) were the first to describe these changes as direct precursors of cancer. HERTIG *et al.* (1949) suggested they be called carcinoma in situ. Follow-up studies of patients with foci of such changes, however, prove they really are **early endometrial adenocarcinoma** (DALLENBACH-HELLWEG, 1979; cf. p. 181).

γ) **Special Forms of Glandular-Cystic Hyperplasia.** The entire endometrium is not always stimulated uniformly by estrogen. Sometimes only certain regions react to the hormone. When the stimulation persists these regions may undergo *focal hyperplasia,* from which polyps may develop or even at times carcinomas, although the remaining endometrium may show regular secretory changes. The focal hyperplasias differ from the diffuse form only in their limitation to a circumscribed region (Fig. 63a).

Hyperplasia of the basalis is not rare. In that condition the cystically dilated and excessively proliferated glands of the basalis push the normal endometrium upward and away (Fig. 63b). Consequently, many cycles may elapse before the hyperplasia makes itself clinically evident (WINTER, 1955). Histologically, the dilated glands are hardly distinguishable from those of the glandular-cystic hyperplasia. In curettings hyperplasia of the basalis can be recognized by its stroma, which usually is irregularly interwoven with bundles of smooth muscle cells but for the basalis still characteristically dense with collagenous fibers. Under appropriate stimulation hyperplasia of the basalis may progress to adenomatous hyperplasia and even to carcinoma. In addition to diffuse hyperplasia of the basalis there are the focal hyperplasias. These may give rise to the formation of socalled endometrial hummocks that may continue to grow, eventually becoming tall polyps.

The polypoid, glandular-cystic hyperplasia is characterized by focal, polypoid growths within the hyperplasia. Some of the glands in these growths dilate cystically and become surrounded by a stroma that is rich in fibers but poor in cells and occasionally very edematous. These polypoid outgrowths are readily recognized by their shape and by the characteristic red of their stroma with the van Gieson stain, owing to the abundance of collagenous fibers. At times the glands within the polyps undergo excessive hyperplasia, a change less disquieting as a precancerous condition than a similar hyperplasia elsewhere in the endometrium. Nevertheless, in a rare polyp extreme glandular hyperplasia may undergo carcinomatous transformation.

At this point in our review we should discuss the **polyps of the endometrium,** which commonly develop from a non-diffuse hyperplasia of the endometrium. These polypoid outgrowths are not neoplasias but rather only focal hyperplasias of the mucosa that develop in circumscribed regions in response to hormonal stimuli. Often they arise from focal hyperplasias of the basalis whence they slowly grow upwards to reach the surface of the endometrium (SCHRÖDER, 1954). At first they have broad bases but with time these become slim stalks, since the normal endometrium about them is shed away during menstruation. Their site of predilection is the endometrium of the fundus and tubal recesses. Based on their histology we distinguish four types of polyps: the glandular, the glandular-cystic, the adenomatous, and the fibrous. For each type there is an equivalent generalized change (that is, type of hyperplasia) that may involve the endometrium diffusely.

The *glandular* polyps resemble the normal endometrium. They are recognized by their loose yet fibrous stroma (seen best with the van Gieson stain) and by their usual refractoriness to cyclic changes. Their glands, having sprouted from the basalis, are clearly proliferating: therefore in a secretory endometrium

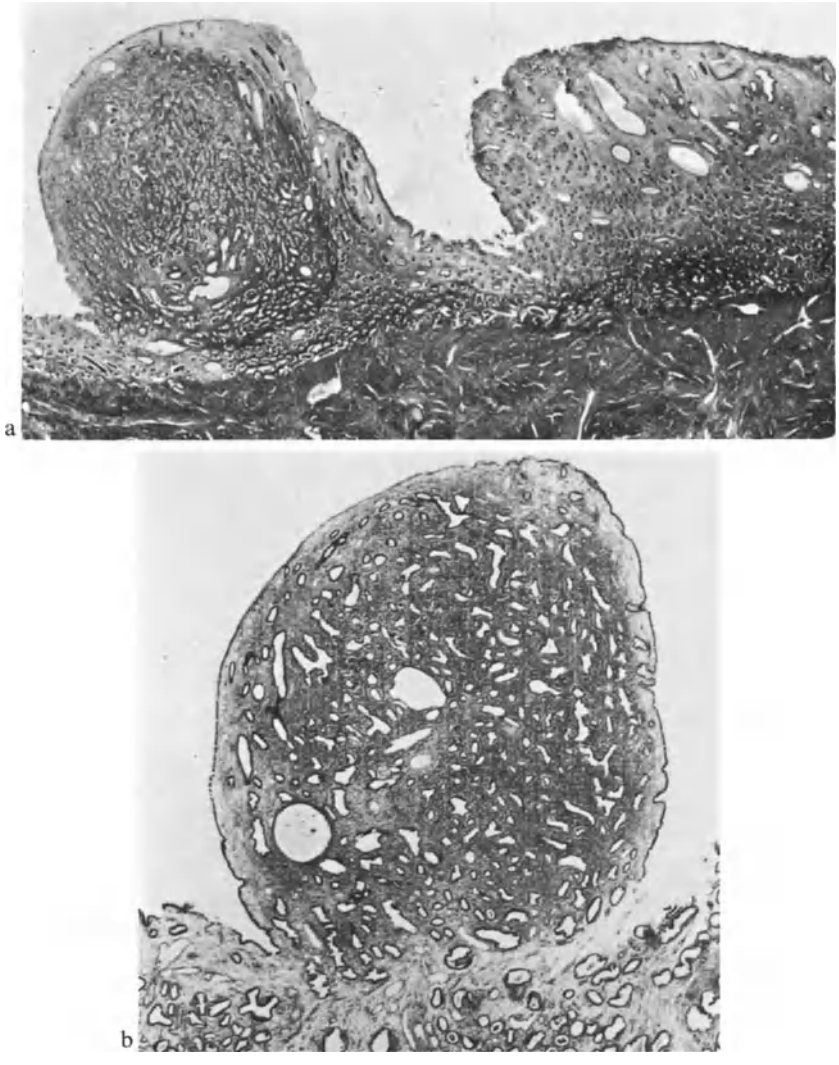


Fig. 64. (a) A large adenomatous polyp arising in a glandular-cystic hyperplasia. (b) A tall, glandular polyp of the corpus endometrium

they will be especially conspicuous and easy to recognize. Often their stroma supports bundles of thick-walled vessels stemming from the basalis. If a polyp remains intact during the curettage then its shape in the sections, with three sides covered by epithelium, will prove diagnostic (Fig. 64). The *glandular-cystic* polyps differ from glandular-cystic hyperplasia only by their more fibrous stroma; the glandular changes in both conditions are alike in all respects. A comparable relationship exists between the *adenomatous* polyps and adenomatous hyperplasia. Yet, these last two conditions do differ biologically. Adenomatous hyperplasia in a single polyp usually has a good prognosis and causes us little concern, whereas diffuse adenomatous hyperplasia has a dubious prognosis, consequently it must be taken seriously. A polyp with a long stalk usually either pulls loose,

or twists and constricts, or undergoes regressive changes. Only when the atypical hyperplastic glands overgrow the stalk does the prognosis become a matter of concern. On the other hand, a carcinoma may certainly arise in a polyp although probably only rarely. It is much more common to find polyps associated with an endometrial carcinoma (according to PETERSON and NOVAK, 1956, in 2.7 per cent of all endometria with polyps and in 15.5 per cent of postmenopausal endometria with polyps). The *fibrous* polyps usually represent regressive forms of the glandular polyps. Consequently we find them most commonly in old women; fibrous polyps are comparable to atrophic endometrium (Fig. 65). In general they have few glands, which may be either cystic or atrophic. The stroma usually consists of parallel bundles of densely packed collagenous fibers, which stain bright red with the van Gieson method. The stroma of the polyps may also contain smooth muscle cells (*adenomyomatous* polyps), indicating that these polyps arose from a focal hyperplasia of the basalis. Some polyps are especially well vascularized (*teleangiectatic* polyps). Their vessels may be either thin-walled capillaries like those of the superficial endometrium, or thick-walled arterioles with narrow lumina like the spiral arterioles.

Theoretically these various polyps may develop at any age. The youngest patient in the series of 1314 polyps described by LAU and STOLL (1962) was twelve years old. The polyps are most common at 50 years of age. After the menopause both the hormonally sensitive adenomatous polyps and the hormonally insensitive "petrified" glandular-cystic polyps (counterparts of regressive hyperplasia) increase in frequency. The latter have flattened epithelial cells and often a hyalinized stroma.

A special form of polyp found in the postmenopausal period was referred to as the "matron's adenoma" or "matron's polyp". Since that term originated clinically and was applied loosely, depending on clinical manifestations, opinions about its histology have varied. Moreover, various investigators have used that name for all polyps occurring after the menopause. In 1922 MENGE classified the matron's adenoma as an actively growing, true neoplasm and separated it from the polyps. Influenced by MENGE's report, BRAITENBERG (1941) described an obvious adenocarcinoma under the expression "proliferating matron's adenoma". Although the prevailing view of ASCHOFF and SCHRÖDER was that all polyps were adenomata, ADLER (1926) pointed to the frequency of polyps in glandular-cystic hyperplasia and suggested that the two conditions had a common etiology. On the other hand, R. MEYER (1923) regarded polyps as circumscribed hyperplasia of the basalis. According to our present concepts the polypoid growths of the endometrium represent local hyperplasias induced by hormones or possibly also by trauma. Therefore, we should like to discard the term "adenoma" and to refer to all benign, localized hyperplasias of the endometrium as polyps. Since the designation "matron's adenoma" appears to be inappropriate for several reasons we prefer to forget it. We suggest instead that all polyps in the postmenopausal period be classified according to their histology into: the adenomatous, the cystic-atrophic, and the fibrous polyps of old age. That classification includes an interpretation about the prognosis, which provides the gynecologist with important information for the therapeutic measures he plans.

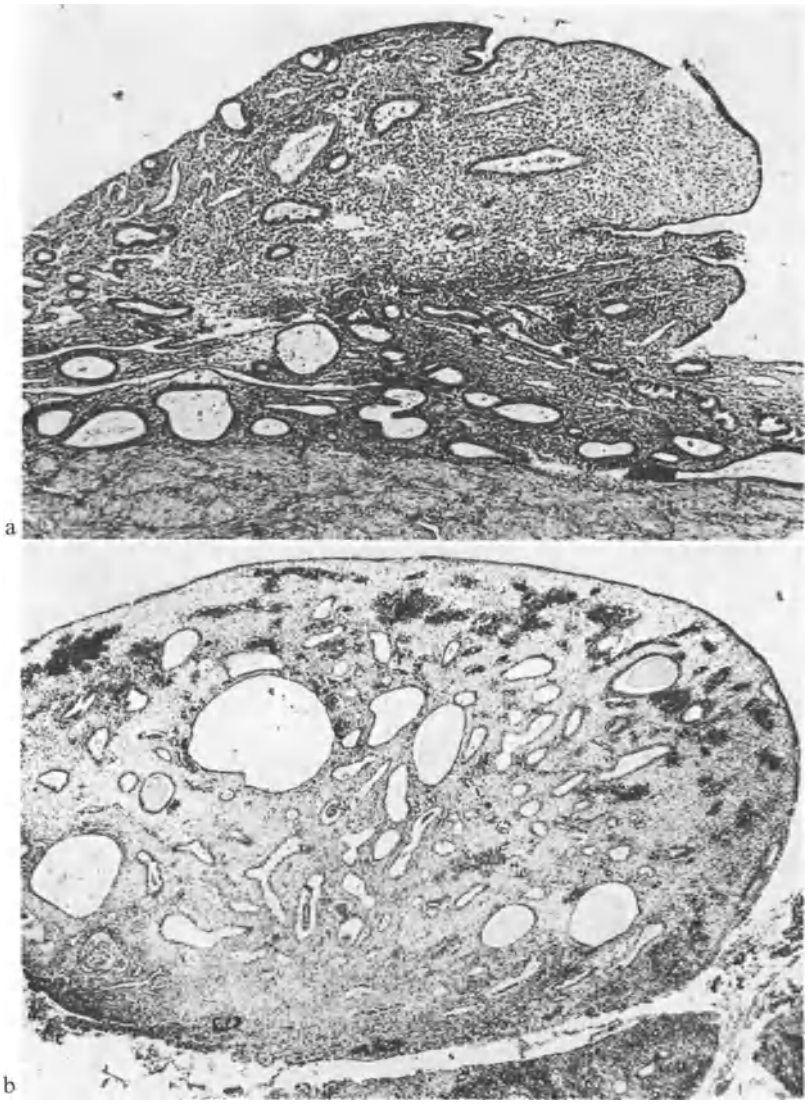


Fig. 65. (a) A broad-based senile polyp with regressive hyperplasia and (b) a fibrocystic senile polyp that has already been shed

Since polyps usually are not discharged during menstruation and may occasionally elude the surgeon's curette, with time they may grow so large as to fill the uterine cavity. Because they are soft and pliable, they generally assume the shape of the cavity. The most important clinical symptoms that polyps produce are interval bleeding, premenstrual and postmenstrual bleeding, and occasionally labor-like pains. Through tension, stretching and pressure, *secondary changes* may develop in polyps, leading to hemorrhage and inflammation, and ultimately to extensive necrosis or diffuse endometritis. At times when the glandular-cystic polyps are traumatized cysts may burst; the mucus extruded into the stroma

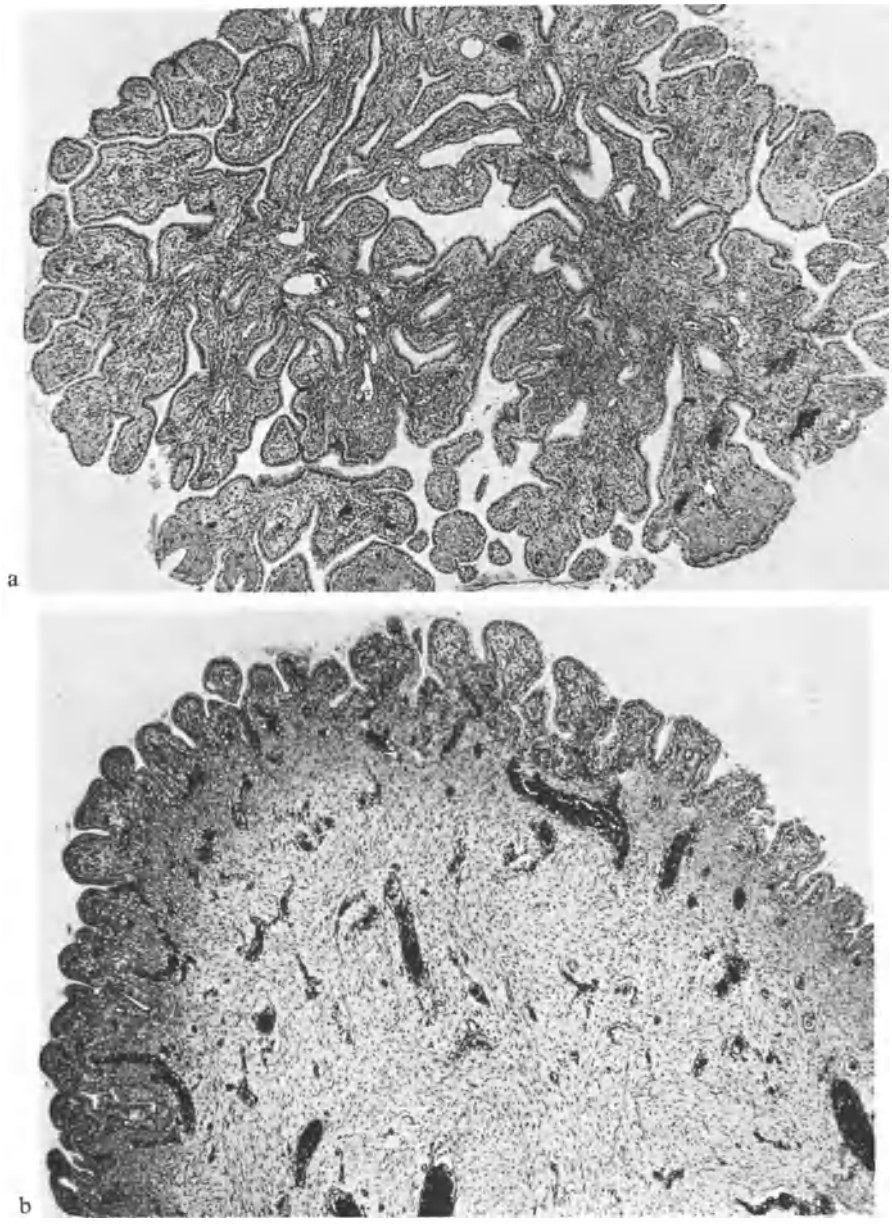


Fig. 66. (a) A papillary polyp and (b) a vascular polyp of the endocervical mucosa

often provokes a granulomatous inflammation (mucus granuloma) (SALM, 1962). Because they tend to persist for long periods, compared with the surrounding endometrium discharged during menstruation, the polyps may become foci of chronic inflammation such as tuberculosis or foreign body granulomata.

Curettings of the endometrial cavity may contain not only parts of endometrial polyps but often fragments of polyps from the endocervix and transitional mucosa.

These fragments may be readily differentiated from the endometrial polyps by the structure of their glands and by the character of their superficial epithelium. The **polyps of the endocervical mucosa** are papillary and covered by a tall, cylindrical, mucus-secreting epithelium (Fig. 66). A similar epithelium lines their glands, which resemble normal glands of the endocervix. Three main types of cervical polyps can be distinguished: the fibrous, the glandular, and the vascular (teleangiectatic). The stromal cells of cervical polyps may undergo decidual change during pregnancy. At times such a change may be the first morphological indication that the patient is pregnant. HARRIS (1958) observed numerous foam cells in the stroma of polyps after prolonged therapy with estrogens. A special type of polyp unusually rich in cellular stroma may develop in girls. Referred to as a juvenile cervical polyp, it must be distinguished from the sarcoma botryoides (TERRUHN, 1977). The glandular and surface epithelium of cervical polyps tends to undergo reserve cell hyperplasia or squamous metaplasia, which by definition is always benign. During a pregnancy (MEINRENKEN 1956), but chiefly during exogenous gestagen therapy, and then often to an extreme degree (cf. p. 246) new glands develop which show a characteristic microalveolar proliferation. When polyps of the cervical mucosa protrude from the cervical os they become either partially or completely covered with metaplastic, squamous epithelium. They are then referred to as *polyps of the portio vaginalis*. The *polyps of the transitional epithelium* present a mixed picture, containing glands not only of the endometrial type but also of the sort found in the endocervical mucosa. Although these polyps are less common than the other types they grow to resemble the others grossly (Fig. 67).

The true or genuine **stromal hyperplasia** of the endometrium is a rare variant of the glandular-cystic hyperplasia and may be regarded as a potential precursor

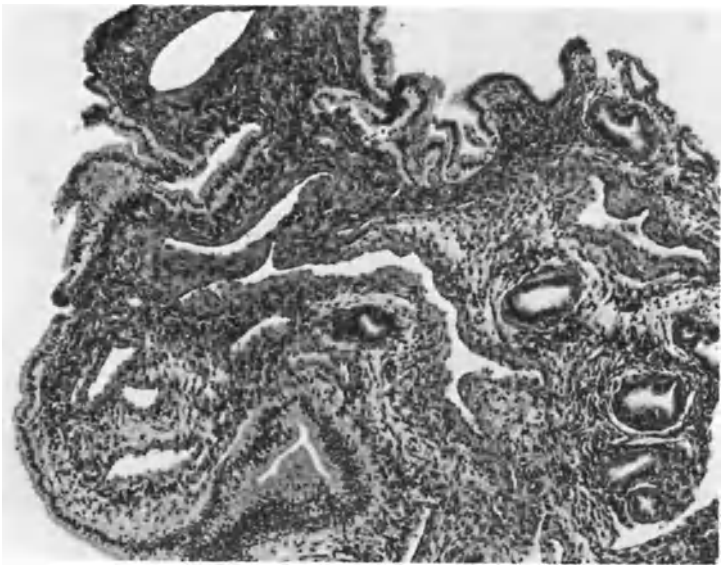


Fig. 67. Polyp of the transitional mucosa. The surface is covered by endocervical epithelium; the glands within the polyp are endometrial

of endometrial sarcoma (HANSON, 1959). The hyperplasia of the stromal cells predominates. These cells have large, often pleomorphic nuclei haphazardly located within sparse cytoplasm. The reticulum fibers between the cells are abundant. The glands become widely separated, are small and narrow, and lined by a single row of epithelial cells (Fig. 68). – A moderate form of stromal hyperplasia with a striking predecidual change of the stromal cells occasionally develops after the treatment of a glandular-cystic hyperplasia with gestagens (see p. 110), or after the use of oral contraceptives (see p. 236), especially those with derivatives of 19-nortestosterone. The sarcoma-like change induced by these hormones may alarm us; however, as of now the change should not be considered as a potential precursor of endometrial sarcoma and should not therefore be confused with true stromal hyperplasia. These interesting experiences with unnatural stimulation of the endometrium with hormones may indicate that a specific (androgenic?) and protracted endogenous disturbance of hormonal balance is responsible for inducing stromal hyperplasia of the endometrium. From the stromal hyperplasia we should furthermore distinguish a common type of hyperplasia with stromal cells arranged in whorls and bound by thickened reticulum fibers. LOHMEYER and VELTEN (1957) found such a hyperplasia in 92 per cent of all uteri with leiomyomata; they believed that when found in curettings it indicated the presence of a submucosal leiomyoma.

d) The Deficient Secretory Phase Associated with Premature Regression of the Corpus Luteum

If the corpus luteum fails to develop normally after ovulation or regresses too quickly, then the stimulatory effect of progesterone on the endometrium becomes deficient. The hormonal balance shifts then in favor of estrogen; consequently, a normal secretory phase cannot evolve. In like manner, development of the secretory phase becomes retarded if the endometrium fails to respond normally to hormonal stimuli, or if the preceding proliferation of the endometrium proved inadequate because too little estrogen had been secreted by the ovaries. Such failures may be due to a central defect in the formation of FSH during the follicular phase, or of LH during the secretory phase, or to an ovarian defect, such as abnormal oocytes that are unable to induce adequate proliferation and luteinization of the granulosa cells. Just as the type and cause of disturbance or interference in the function of the corpus luteum may vary, so may the histological picture of the resultant deficient secretory phase fluctuate. One has the best chance of diagnosing the changes that occur by examining tissue taken at the end of the secretory phase. The specimen obtained should be from the uterine fundus, since the cyclic changes in the endometrium near the uterine isthmus may be delayed or imperfectly developed, even normally. Because the degree of secretory differentiation may vary greatly from one cycle to the next, depending on the variable insufficiency of each corpus luteum developing, proper evaluation of the patient requires biopsy material from at least two cycles. When we apply strict criteria, we find that a deficient secretory phase due to endogenous disturbances is more common than previously assumed; although ISRAEL (1959) reported

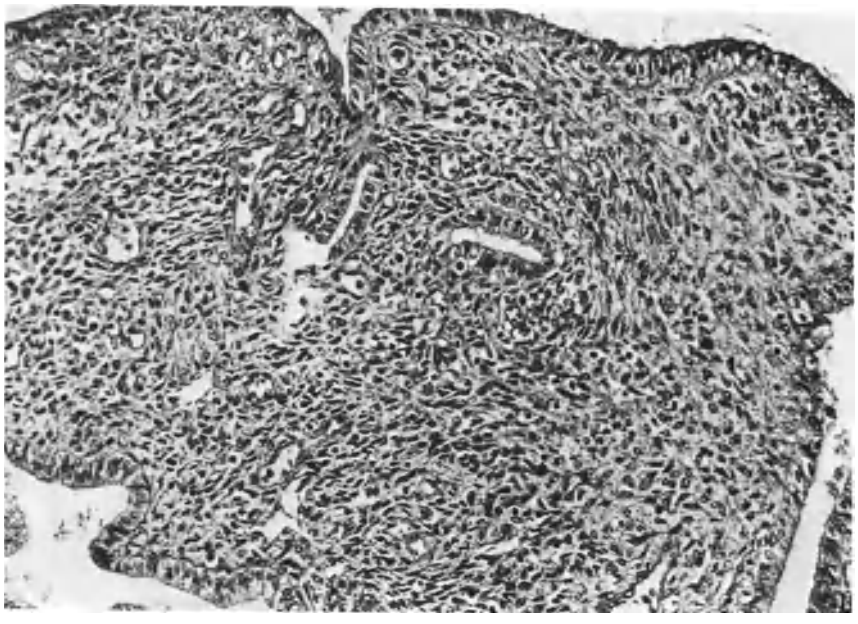


Fig. 68. Stromal hyperplasia of the endometrium. The stromal cells have large polygonal nuclei. The glands are sparse

it in only 3.5 per cent of his sterility patients, we found it in 20 per cent of our sterility patients (SILLO-SEIDL and DALLENBACH-HELLWEG, 1974).

By carefully correlating clinical and histological findings, GIGON *et al.* (1970) were able to divide the deficient secretory phase into three types of different causes (see Table 8a). From their proposal it is obvious that one cannot histologically diagnose a coordinated delay in the maturation of the endometrium without knowing the day of the cycle, since that delay in maturation is the only histological criterion for distinguishing it from a normal secretory phase. On the other hand, the deficient secretory phase of type 3, the most common type, has a characteristic histologic picture.

Although histological sections stained with hematoxylin-eosin prove adequate for revealing many of the changes, other changes can be detected only with histochemical methods. An example of a change readily distinguished histologically is the finding of an early secretory phase at the onset of menstruation. Another example is to find that the development of glands and stroma varies from region to region, and that the glands are at a stage of development different from that of their stroma (they are "out of phase" or discordant). Adjacent to normal secretory *glands* that correspond with the proper day of the cycle one may see other glands that are poorly developed or deficient, with basal vacuoles and small rounded nuclei in low, functionally-inactive epithelial cells (Fig. 69). Other glands however may be in the proliferative phase and contain elongated nuclei with dense chromatin in a non-functioning, hormonally nonresponsive epithelium. The variation in glandular differentiation results from de-

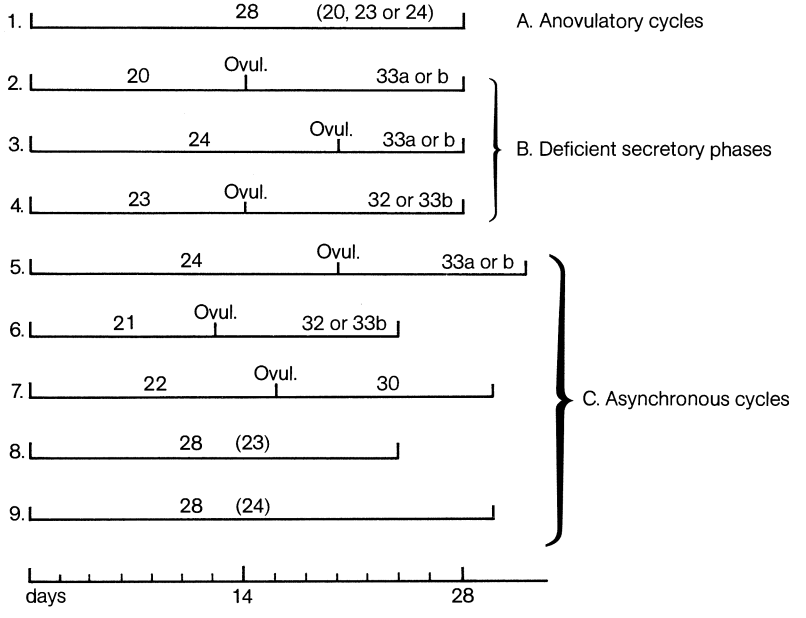
Table 8a. Various types of corpus luteum insufficiency causing a deficient secretory phase

Group	Basal temperature	Gonadotropins	Urinary excretion of pregnandiol	Time of ovulation	Development of the corpus luteum	Endometrium	Cause	Therapy
1	biphasic, late rise	without LH peak	low	delayed	shortened	apparently delayed, coordinated ripening of glands and stroma	central (deficient stimulation of corpus luteum)	chlomiphene, gonadotropin
2	biphasic, stair case rise	within normal range	low	at proper time	deficient	truly delayed, coordinated ripening of glands and stroma	ovarian (corpus luteum insufficiency)	progesterone
3	biphasic	variable	normal	variable	regular	delayed and dissociated ripening of glands and stroma; often polyps	endogenous estrogen predominant	progesterone

creased progesterone levels. Only those portions close to the blood supply (spiral arterioles) receive enough progesterone to react properly. In contrast, when levels of progesterone are normal, all parts of the endometrium, including those more remote from the arterioles, are stimulated (ULM, 1970). Accordingly, with deficient levels of progesterone, the epithelium of the glands will contain variable though diminished amounts of glycogen, mucopolysaccharides, proteins and acid phosphatase. The activity of the alkaline phosphatase is often increased (NOYES, 1959; SCHMIDT-MATTHIESEN, 1965; further literature op. cit.). Electron-microscopically the granules of glycogen, the mitochondria, and the intra-nucleolar channel system of the glandular cells are clearly reduced in size and number (ANCLA *et al.*, 1967; GORE and GORDON, 1974). The concentrations of estrogen receptors in the nucleus and cytoplasm are lower than in the normal secretory phase. The concentrations of progesterone receptors correspond with the low values of the late secretory phase.

The *stroma* may be either poorly differentiated, arrested at about the grade of maturity of the early proliferative phase, or it may be edematous, as it is premenstrually, but reveal no predecidual change. On the other hand, it may be flecked with focal regions of predecidual change, localized edema, and small

Table 8 b. Possible variations of endometrial function in sterility (for the numbers see Table 3)



A 1: Anovulatory cycle with cyclic (*20*), deficient (*23*) or irregular (*24*) proliferation.
B 2: Apparently delayed, coordinated (*33a*) or dissociated (*33b*) deficient secretion following cyclic proliferation (*20*).
3: Truly delayed, coordinated (*33a*) or dissociated (*33b*) deficient secretion following irregular proliferation (*24*) with delayed ovulation and early breakdown.
4: Abortive (*32*) or deficient and dissociated (*33b*) secretion following deficient proliferation (*23*).
C 5: Prolonged cycle, as in B 3, but without early breakdown.
6: Shortened cycle with early ovulation following deficient proliferation (*21*), secretory phase as in B 4, or shorter.
7: Prolonged, otherwise normal cycle (*22* and *30*) with delayed ovulation.
8: Shortened anovulatory cycle with deficient proliferation (*23*).
9: Prolonged anovulatory cycle with irregular proliferation (*24*)

hemorrhages. At times the stroma contains large amounts of glycogen prematurely, or accumulates acid mucopolysaccharides focally. The ground substance, which normally undergoes two major transformations during the menstrual cycle, may fail to change or may remain depolymerized during the entire secretory phase. That depolymerized state apparently is associated with the focal accumulation of glycogen in the stroma (SCHMIDT-MATTHIESEN, 1965). Occasionally a widespread pathological edema develops. The spiral arterioles remain small and under-developed.

Twenty-five per cent of all deficient secretory phases are abnormally short. They at times last only eight days (BUXTON, 1950), as concurrent studies of the ovaries have shown. The shedding of the endometrium takes place prematurely

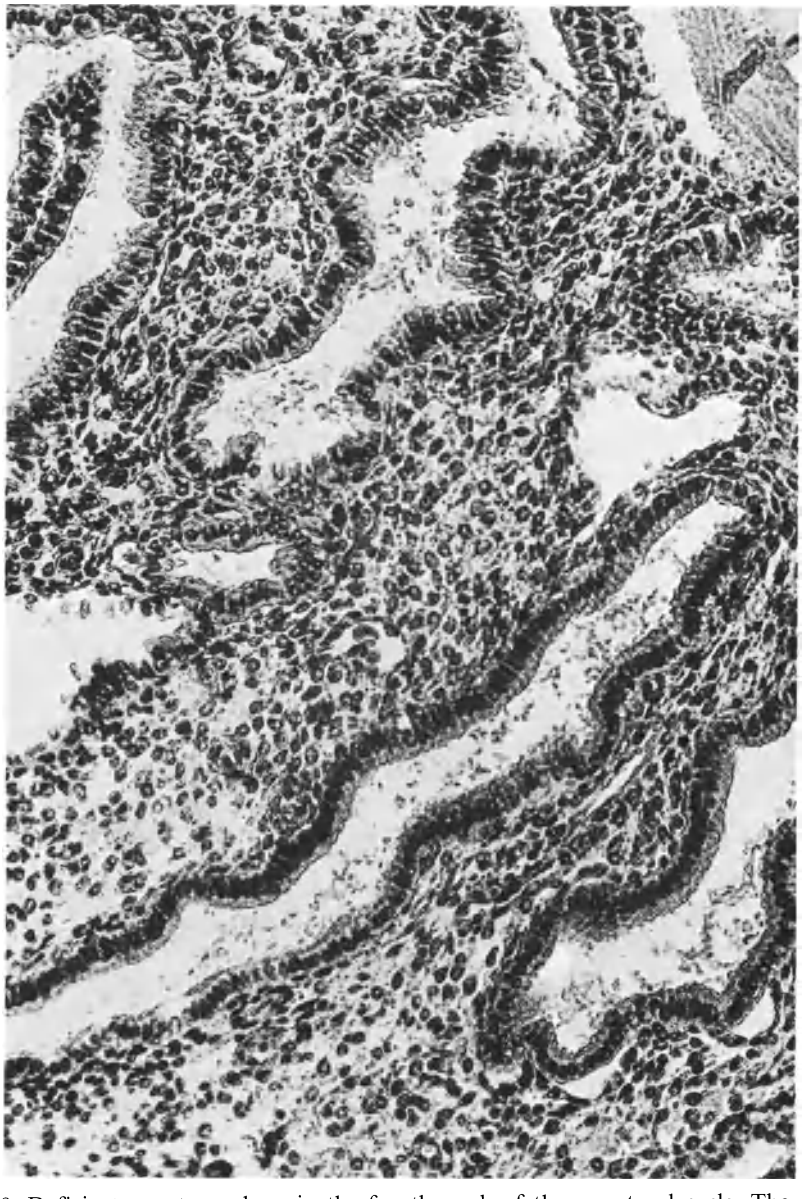


Fig. 69. Deficient secretory phase in the fourth week of the menstrual cycle. The glands are only slightly tortuous and lined with low epithelial cells that have elongated, dense nuclei. The stroma is loose and poorly differentiated

because the levels of progesterone decline before they should owing to the abnormal corpus luteum. A menstrual shedding with correct dissolution of stromal and glandular elements can take place only when progesterone has acted on the endometrium for at least 10 days. The deficient secretory phase may also terminate in pathological bleeding due to estrogen withdrawal (fall in estrogen levels); such bleeding occasionally develops late but is usually prolonged. In general, good therapeutic results may be obtained by administering progesterone during the last week of the menstrual cycle (MOSZKOWSKI *et al.*, 1962). That is best given parenterally, since gestagens taken orally depress the production of endogenous progesterones (SOULES *et al.*, 1977). Such a treatment has led to a pregnancy rate of 50% after an average of five menstrual cycles. If the cause of the deficient secretory phase is central then gonadotropin or clomiphene may prove beneficial (DE MORAES-RUEHSEN *et al.*, 1969; LEIDENBERGER, 1976; see Table 8a).

e) The Endometrium Associated with Persistent Corpus Luteum

α) If a corpus luteum develops normally after ovulation but fails to regress later at the proper time because of disturbances of the hormonal mechanisms controlling it, then it continues to secrete progesterone. As a consequence, the changes normally brought about in the endometrium by the decline in progesterone shortly before menstruation fail to develop or do so late; **"irregular shedding"** of the endometrium results. The menstrual bleeding may start at the proper time or may be delayed. In any case, it is prolonged and usually excessive. Persistence of the corpus luteum may be induced by hyperstimulation either from hypophyseal gonadotropin or from placental gonadotropin; that is, by an intra-uterine or extra-uterine pregnancy with increased secretion of gonadotropin. In extreme cases, a hydatidiform mole may cause several corpora lutea to become cystic. MCKELVEY and SAMUELS (1947) commonly observed irregular shedding during the first postpartum menstruation, perhaps because the hypophysis failed then to function properly. Similar endometrial changes may be induced by spontaneous polyovulation (PEPLER and FOUCHE, 1968) or by therapy with gestagens, as HOLMSTROM and MCLENNAN (1947) were able to demonstrate by injecting progesterone during the menses, and as results with some of the oral contraceptives have proved. It is logical therefore that an irregular shedding may be prevented by giving estrogen two days before the onset of menstruation (WEBER, 1954). After the diagnosis of irregular shedding is verified histologically, if its cause remains clinically obscure, then all the various etiological possibilities just reviewed should be considered.

Irregular shedding was recognized by DRIESSEN in 1914 and described thoroughly by PANKOW in 1924 and by BANIECKI in 1928. The condition develops only during the reproductive years, predominately between the ages of 25–50 years (MCKELVEY, 1942: 30–50 years; STADTMÜLLER, 1950: 25–30 years and 40–45 years; THIERY, 1955: 24–40 years). Irregular shedding occurs either at every menstrual period or only once, as for example, after a stillbirth or after a clinically unrecognized abortion of a blighted ovum. BANIECKI observed irregular shedding 61 times among 465 curettings.

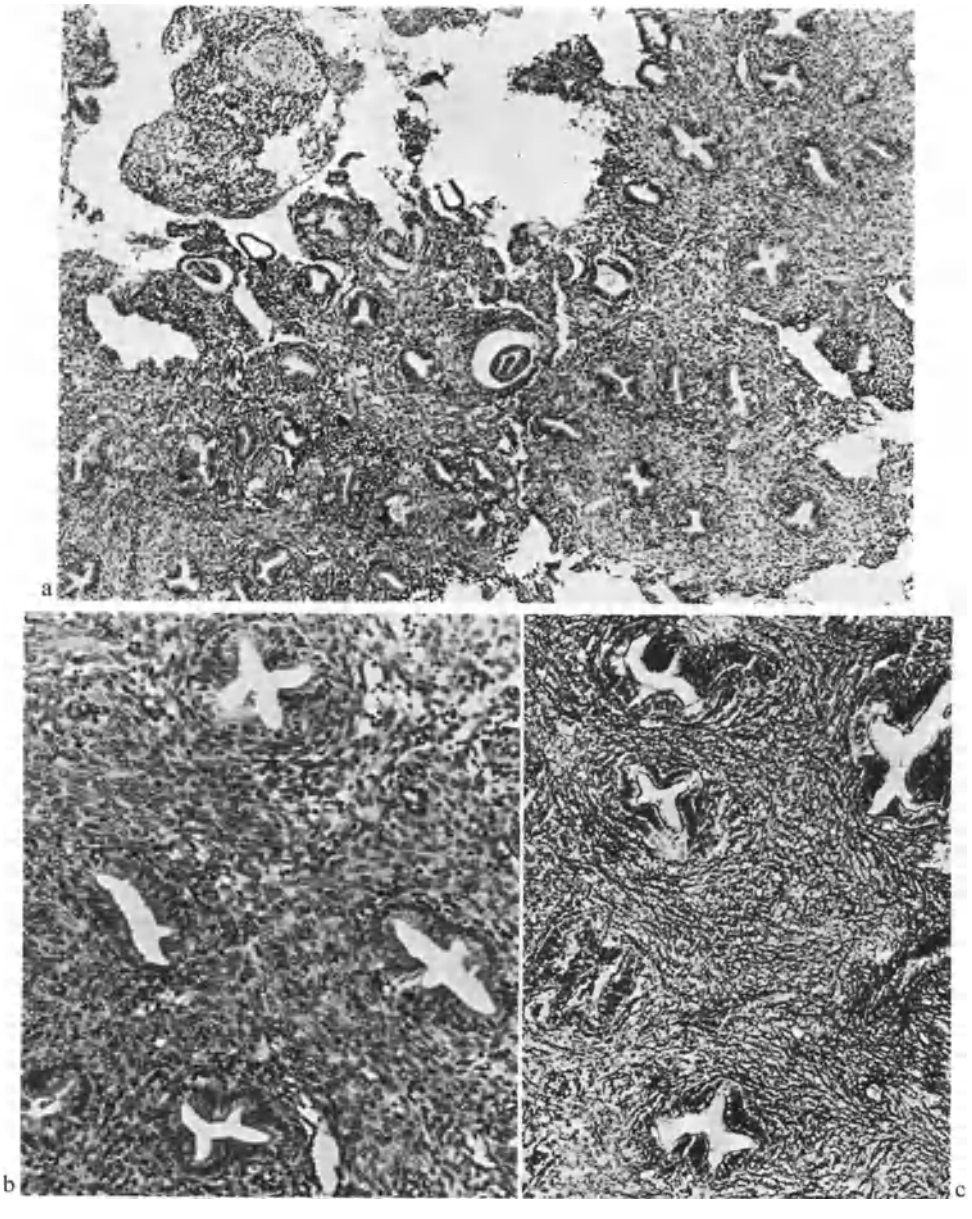


Fig. 70a–c. Irregular shedding of the endometrium. (a) Survey view of the usual disordered appearance of focal dissolution and desquamation. (b) Higher magnification: the star-shaped glands are embedded in a stroma of large cells. (c) The network of reticulum fibers is intact and dense (silver impregnation after GOMORI)

The *histological recognition* of irregular shedding is not easy for the inexperienced since the histological changes are confusing. It is exactly that confusion of the histological picture, however, that should make us think of irregular shedding. Characteristic of the condition is the diverse admixture of endometrial

fragments in various stages of regression and dissociation still evident several days after menstruation started. The changes cannot be diagnosed in the intervals between bleeding or just after its onset. Since the levels of progesterone do not fall, the premenstrual release of relaxin and proteolytic enzymes is prevented, and consequently the reticulum network fails to undergo dissolution (DALLENBACH-HELLWEG and BORNEBUSCH, 1970). The normally developed endometrium cannot disintegrate; it merely shrinks owing to the loss of water induced by the decrease in estrogen. Since the shedding is greatly prolonged, the regressive changes in the glands and stroma become more intense. Then too, because the resulting changes lag in time they appear much more striking than those normally seen before or during a regular menstruation.

The most characteristic sign of irregular shedding, readily seen under low magnification, is the narrow, star-shaped appearance of the *glandular* lumina (Figs. 70 and 71). The cytoplasm of many of the glandular cells is clear and often contains abundant glycogen, thus contrasting sharply with the surrounding small stromal cells that have scanty, dark cytoplasm and densely packed nuclei rich in chromatin. Often the nuclei of the glandular cells are equally shrunken with dense chromatin, but owing to the excessive hormonal stimulation they may also be enlarged, grotesquely shaped, and suspended haphazardly within a swollen, clear cytoplasm (Fig. 127). Such a phenomenon, first described by ARIAS-STELLA in 1954, is associated with an abnormally high level of gonadotropin and is, therefore, a sign of a dead fetus with continued production of the hormone by a trophoblast that remains viable (see p. 263). A positive Arias-Stella phenomenon, consequently, is to be expected in only some of the cases of irregular shedding of the endometrium. If the phenomenon is found, then the irregular shedding

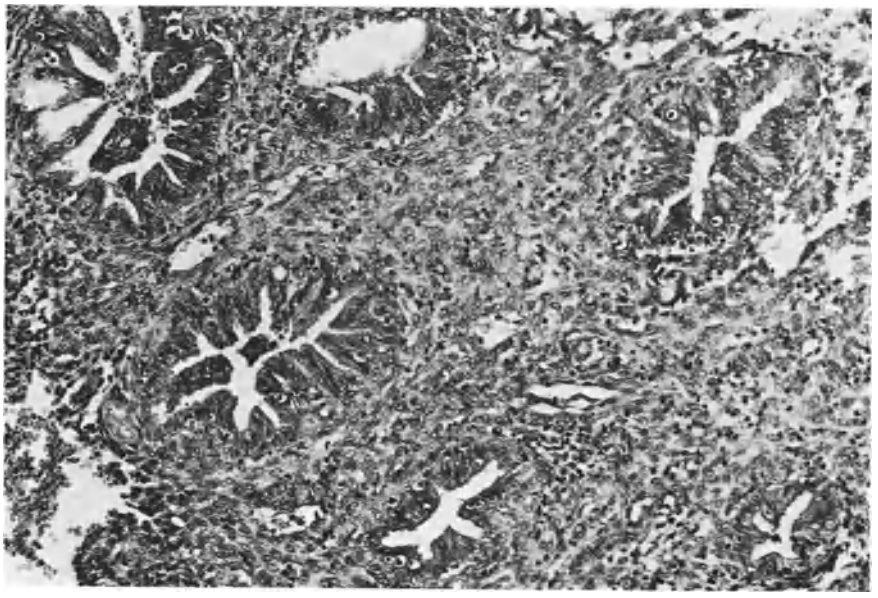


Fig. 71. Irregular shedding, advanced stage. The typical star-like shape of the glands is conspicuous. The surrounding stroma is dense and rich in fibers

may be related to death of a fetus even though trophoblasts or decidual cells are histologically lacking (see also OVERBECK, 1959).

The dense *stroma* of these portions of endometrium is composed initially of large, compact cells and many granulocytes. Later after shrinkage takes place, the granulocytes appear more numerous than in a premenstrual stroma or in an intact decidua. Most of the granulocytes are ladened with granules that are never discharged. Silver impregnation reveals an intact, tightly knit meshwork of reticulum fibers woven about the stromal cells and glands, holding them firmly in place. The spiral arterioles slowly undergo retrograde changes after the elastic fibers in their walls gradually degenerate (THIERY, 1955). In the endometrium of young women with irregular shedding, BANIECKI (1928) observed that the dilated and tortuous spiral arterioles were often thrombosed because of the slow involution and prolonged bleeding; in contrast, he found that in patients in the preclimacterium the arterioles were generally narrow. The stromal cells about the arterioles remain intact the longest. Otherwise, the stromal cells undergo retrograde changes and shrinkage before the epithelial cells of the glands do. In brief, the sequence in the protracted involution is as follows: first stromal cells, then glandular epithelial cells, then blood vessels.

Besides these characteristic changes in some parts of the endometrium, other regions may be found that have already undergone extensive dissolution and hemorrhage. It is possible that in these regions the shrinkage of the endometrium had produced local ischemia, cutting off the supply of progesterone. Thus the granulocytes are induced to release their granules of relaxin and the reticulum fibers in these regions disintegrate, as in a normal menstruating endometrium. Between these two extremes—the intensely shrunken but intact endometrium and the normal menstruating endometrium—all transitions may be found. Further, when the bleeding is particularly protracted, other regions of the endometrium may already have begun to regenerate and may show early proliferative changes of the next menstrual cycle. These parts are recognized by the loose, edematous stroma composed of poorly differentiated spindly cells and a reticulum network of sparse, delicate fibers. The glands are narrow, straight and lined by a uniform row of inactive-appearing epithelial cells. At times the parts of endometrium undergoing the protracted irregular shedding cover in cap-like fashion the regions of regenerating endometrium (Fig. 72). In rare instances the degenerating parts fuse with the regenerating tissue and become organized. Regeneration of the superficial epithelium takes place only after complete detachment of the menstruating endometrium; consequently, the regeneration is greatly prolonged.

Depending upon the intensity and quality of the hormonal stimulus still persisting or upon the speed with which it abates, the regressive and progressive changes just described may accordingly vary in extent and kind. One of the components of the endometrium may change more than the others. Borderline cases may show changes that merge gradually with those of a normal menstruation. In differentiating irregular shedding from protracted bleeding due to other causes, it is important to demonstrate that the glandular *and* stromal cells clearly show secretory (progestational) effect.

It may be possible histologically to draw conclusions about the *etiology* of

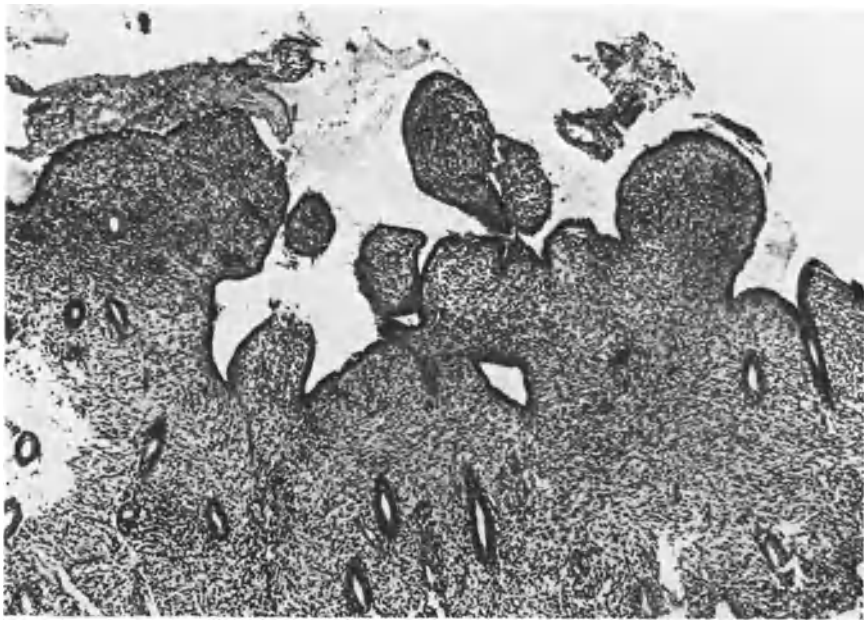


Fig. 72. Advanced stage of irregular shedding that developed after use of oral contraceptive agents. The humped remnants of the old mucosa rest on newly proliferating parts

irregular shedding by disclosing endometritis, hyalinized arterioles, and necrotic or degenerated remnants of decidua, placental villi, trophoblasts or an Arias-Stella phenomenon. Some of the degenerating glands may dilate cystically after the fetus dies, whereas the regressing glands of irregular shedding due to other causes usually remain small. In curettings it may be exceedingly difficult to differentiate the cystic, degenerative changes occurring post-abortum from those of a hemorrhagic, glandular-cystic hyperplasia in secretory transformation. Accurate clinical information is extremely helpful here. Occasionally the use of oral contraceptives may lead to irregular shedding of the endometrium, since they may induce a deficiency in progesterone resulting in an insufficiency of endometrial granulocytes and consequently of relaxin. The reticulum fibers therefore fail to undergo dissolution. If, however, such histological clues are lacking, then the genesis of the irregular shedding must be explained clinically. Precise clinical data are exceedingly valuable in the accurate interpretation of regressive changes of the endometrium. Without knowledge of the menstrual cycle it may be impossible to differentiate a prolonged menstruation from the terminal, late discharge of a decidualized endometrium associated with an extrauterine pregnancy (Hinz, 1954). The cause of the irregular shedding can be clarified in most cases, or at least inferred, if information about the duration of endometrial bleeding, about pregnancy tests and about urinary excretion of hormones is correlated with the results of the histological studies.

Irregular shedding may also follow a persistent, but previously insufficient corpus luteum, which may develop post partum or during the climacterium.

If such an insufficient corpus luteum persists, the endometrial histology varies slightly from the classical picture of irregular shedding: some of the collapsed glands still reveal signs of abortive secretion while neighbouring glands may show no such evidence although surrounded by focal hemorrhagic necrosis. This variety of irregular shedding is usually recognized only by the experienced pathologist; its identification, however, is important for correct treatment of the patient.

*β)*Within the spectrum of irregular shedding **dysmenorrhoea membranacea** represents a special entity. According to DEELMAN (1933) that term was first used by MORGAGNI in 1723. Pathologically, what is meant is a spontaneous slough of the endometrium in one cylindrical piece or in large membranous pieces that retain the shape of the uterine cavity. Histologically, the tissue consists of corpus endometrium in either the predecidual or the decidual state. It is variably infiltrated with polymorphonuclear leucocytes and in the process of dissolution. The decidual cells may disclose advanced retrogressive changes and often have spindly shapes. The endometrial granulocytes are generally very numerous and retain their granules. The glands are lined by low cuboidal cells whose small, rounded nuclei appear like a chain of beads.—The causes for this condition are the same as those for irregular shedding. GREENBLATT *et al.* (1954) and PANELLA (1960) observed the discharge of a decidual cast after administering progesterone. The associated dysmenorrhea is probably due to the failure of the tissue to undergo dissolution. Relaxin is not released since the level of progesterone fails to decrease. A decidual cast may be expelled under similar conditions after an abortion. It remains unclear, however, how despite the elevated level of progesterone the decidualized endometrium spontaneously detaches without first undergoing dissolution. One may postulate that the fall in progesterone takes place too late, at a refractory phase when dissolution of the tissue cannot occur. The only response possible is the complete discharge of the intact endometrium.

If the progesterone fails to fall, then with time it stimulates the stromal cells to transform into decidual cells, although no pregnancy exists. The decidua that forms cannot be distinguished from that of a pregnancy. Such cases are reported from time to time. SPECHTER (1953) found a typical decidua in two young women who had persistent corpora lutea, and once in a 71 year old woman with a carcinoma of the ovary. We have seen similar cases. On the other hand, decidual transformation of the stroma may develop concurrently with atrophy of the glands, resulting in "arrested secretion" (see p. 221). That condition is seen only after stimulation with exogenous gestagens. One of our patients, a 60 year old woman who had received progesterone over a long time for endometriosis, developed a perfect decidua that contained great numbers of granulocytes but atrophic glands (Fig. 109). Such a decidua may also be detached in large membranous pieces.

Occasionally one finds that patients in the preclimacteric or climacteric periods have a tall secretory endometrium, which may measure one centimeter or more in height, resembling the endometrium found about ten days after successful implantation of a blastocyst. The glands are highly secretory. Only some of their epithelial cells indicate excessive hormonal stimulation, appearing thereby

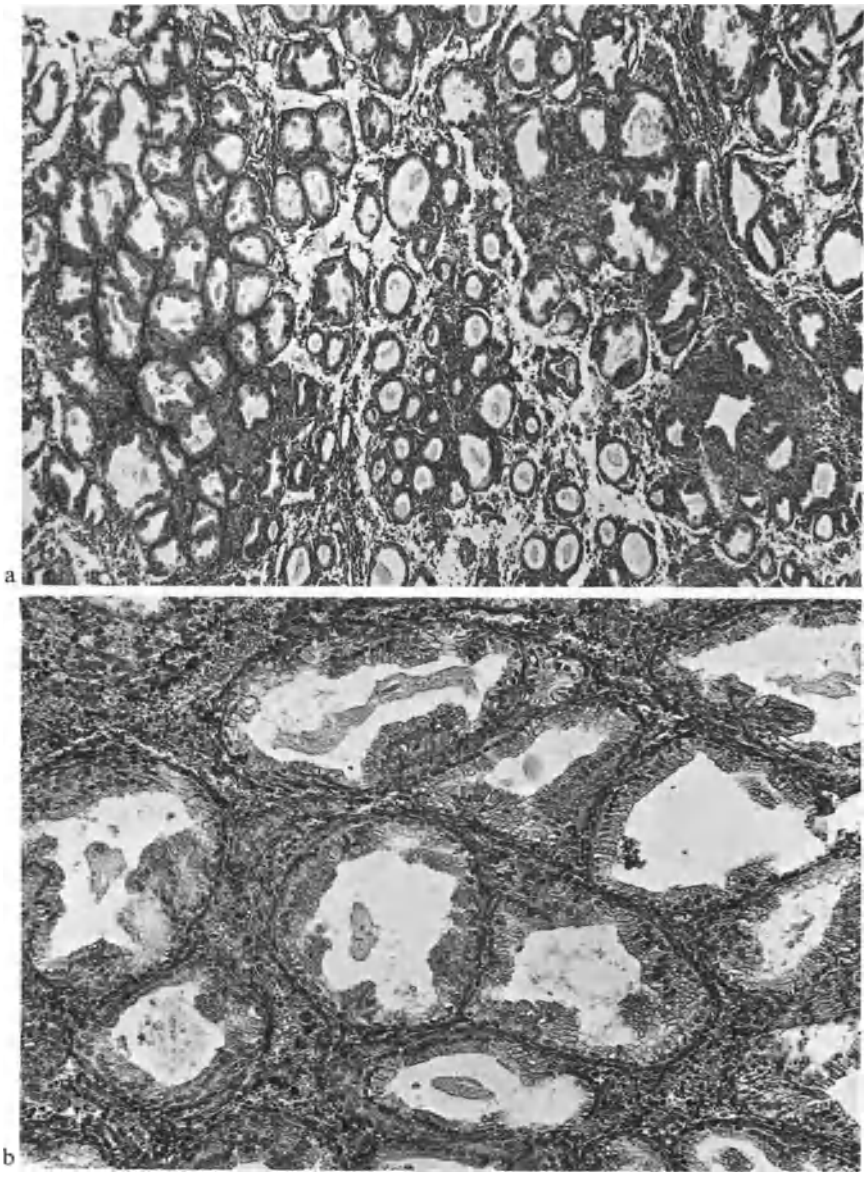


Fig. 73a and b. Secretory hypertrophy. Characteristics are the hypersecretory glands varying in diameter and distribution; the surrounding stroma reveals either edema or predecidual change. (a) Low magnification. (b) High magnification

unusually large and clear with prominent, irregular nuclei rich in chromatin. The stroma is predecidual, very loose and focally edematous (Fig. 73). The spiral arterioles are greatly hypertrophied and proliferated. We classify these changes under the term of **secretory hypertrophy.** We surmise the condition results from

a hormonal imbalance during the preclimacteric period, either from excess production of hypophyseal gonadotropin or from hyperfunction of a corpus luteum (see p. 145).

f) The Endometrium Associated with Sterility

Normal implantation of the fertilized ovum depends on a precise physiological balance between numerous factors of structural and functional nature. Consequently, it is easy to understand how many different and unrelated disturbances can give rise to sterility. If we disregard disturbances causing sterility in the husband, then those arising in the patient may involve any part of her genital system or parts of her central nervous system that hormonally control the ovaries. Here I shall discuss only those causes of sterility that can be diagnosed from the characteristic changes they produce in the endometrium. We should emphasize, however, that if we exclude chromosomal abnormalities, then almost all disturbances of the genital organs can lead to structural changes in the endometrium.

To clarify causes of sterility, the clinician has available an impressive array of diagnostic tests to choose from. Because the newer methods for measuring hormones in the blood are much more accurate than those used fifteen to twenty years ago (GEIGER, 1980), they have contributed much in our understanding of the secretion and interrelationships between hormones. Levels of hormones do fluctuate, sometimes only briefly, sometimes for longer circadian periods. Such fluctuations help to explain discrepancies occasionally noted between plasma hormone levels and histological dating of endometrial maturation. The most reliable method for making a functional diagnosis of the endometrium, therefore, remains the histological study of a "strip" biopsy if performed by a pathologist experienced in this special field. Clinical investigators express the same opinion (ANNOS *et al.*, 1980; ROSENFELD *et al.*, 1980). To be able to carry out his study accurately, however, the pathologist must know about the patient's menstrual cycle, about on what day of her cycle the biopsy was made, and about any hormones she may have received. As prerequisite for the clinician, he should obtain the "strip" biopsy at the end of the menstrual cycle; that is, premenstrually or at the onset of menstrual bleeding. If one finds a normal secretory endometrium, or a secretory endometrium undergoing normal involutional changes, corresponding to the day of the cycle, then the cause of the sterility is not in the endometrium but should be looked for elsewhere. We should not forget, however, that when the functional disturbances are slight, normal cycles may alternate with abnormal cycles. In such instances, it is advisable to repeat the "strip" biopsy in subsequent cycles. – In addition to the functional diagnosis, the histological study may reveal unexpected inflammations of the endometrium, such as tuberculosis, or even polyps and tumors. – Moreover, the "strip" biopsy can supply tissue for determining progesterone receptors, which might help to explain a discrepancy between elevated serum levels of progesterone and a proliferative endometrium.

As indicated by the figures published by different investigators, the frequency of pathological changes of the endometrium in sterility varies greatly. No doubt

the frequency depends to a large extent on the skill employed in preparing the histological sections of the endometrium, and on the experience and knowledge of the pathologist who studies them. According to VACZY and SCIPIADES (1949), HINZ (1953), and FOSS *et al.* (1958), 15–20 per cent of all sterile women have an anatomical or functional disturbance of the endometrium. STAFFELDT and LÜBKE (1967) specify 25 per cent; KANTOR and HARREL (1953) 25.9 per cent. According to SILLO-SEIDL (1971), the percentage is 46 per cent. ROMAN and LABAEYE (1964) found endometrial disturbances in 54.8 per cent of all sterile women. The disturbances manifest themselves in many different ways. In some instances, however, although the functional disturbances causing the infertility may subtly differ, the morphological changes they induce in the endometrium may be similar. Only by carrying out additional clinical, biochemical and endocrinological studies is it possible to clarify these subtle differences and precisely define the cause of the sterility (see Tab. 9).

The menstrual cycle may vary in length **(asynchronous cycles)** without the histological appearance of the endometrium deviating significantly from that of a normal cycle. Without a clinical history, therefore, it is impossible to diagnose variations in the cycle. Since both a short cycle and a prolonged cycle may be the only cause of the sterility, it is exactly for such abnormal cycles that the correlation of clinical data with the results of histological studies is of paramount importance. Only after the cause of the variation in the cycle has been clarified can a rational therapy be instituted.

Such a shift in a menstrual cycle although the endometrium is otherwise normal, is enough to alter the attraction of the endometrial tissue for the blastocyst on the day of implantation (FOSS *et al.*, 1958; found by STAFFELDT and LÜBKE in 10 per cent of their sterility cases). What conditions that attraction are the chemical and structural changes induced by the postovulatory rise in plasma progesterone. It must reach a precise level if the blastocyst is to be able to imbed at the proper time (BEIER, 1981). Only with precise knowledge of the daily changes occurring during the menstrual cycle ("histological dating of the endometrium" — NOYES and HAMAN, 1953) can such functional disturbances be detected. The asynchrony usually is due to a central dysfunction such as a juvenile hypofunction of the hypothalamus or a premature menopause, both of which may induce either deficient or excessive gonadotropic stimulation of the ovary (GEIGER, 1980).

When the menstrual *cycle is shortened,* then ovulation may take place prematurely. The subsequent secretory phase, however, remains deficient since the endometrial tissues that normally differentiate under the effects of progesterone to prepare for nidation cannot develop completely because the preceding proliferation was inadequate. In other instances the proliferative phase may be of normal duration but the secretory phase shortened owing to premature regression of the corpus luteum. Under both circumstances we will find that the secretory phase is deficient shortly before menstruation (see p. 129). ROSENFELD and GARCIA (1976) reported that 36% of their 238 infertile patients had shortened menstrual cycles, whereas in only 3% were the cycles prolonged.

The *prolonged menstrual cycle* may also have various causes (PLOTZ, 1950). On the one hand, the Graafian follicle may persist for about three weeks and

Table 9. Functional disturbances of the endometrium in infertility

Morphology	Possible causes
Atrophy	a) non-functioning ovaries (central or ovarian defect) b) refractive endometrium
Insufficient proliferation	a) Deficient follicular stimulation (central or ovarian defect) b) Anovulatory cycle
Irregular proliferation or hyperplasia	a) Persistent follicle b) Repeated anovulatory cycles (polycystic ovaries) c) Endometrium refractive to progesterone
Deficient secretory phase a) with coordinated delay b) with dissociated delay	a) Insufficient corpus luteum (central or ovarian defect) b) relative corpus luteum insuffiency due to high endogenous estrogen
Abortive secretion	non-ovulating, insufficient follicle with sporadic luteinization
Arrested secretion	gestagen stimulation without ovulation, mostly exogenic
Asynchronous cycle	Disturbance of central regulation (direct or indirect by negative feedback mechanism)

be followed by a normal or abbreviated secretory phase. In that event, delayed ovulation may lead to intrafollicular overripeness of the ovum which results in sterility (see below). On the other hand, a persisting follicle tends to induce a protracted anovulatory cycle. Another possibility is irregular shedding of the endometrium associated with a persistent corpus luteum. As already mentioned, these various possibilities can be clearly differentiated if a curettage is performed premenstrually or just before the onset of bleeding, and the results correlated with those of vaginal cytology and with the clinical history (see Table 8 b).

If the menstrual cycles are of normal duration, then either a **deficient**, or **delayed** or **absent secretory phase** usually is responsible for the sterility, as in an anovulatory cycle or an insufficiency of the corpus luteum (Overstreet, 1948; Döring, 1968), or when the endometrium fails to respond to the circulating progesterone (Cooke *et al.*, 1972). Since these abnormal cycles may occur regularly or may fluctuate with normal cycles (Stevenson, 1965), the histological proof of a normal secretory endometrium provides little information for prognosing the course of the next cycle. Only careful measurement of the basal temperature (Rust, 1979) and repeated curettages or endometrial biopsies can clarify matters. Histochemically, the content of glycogen is usually diminished (Hughes *et al.*, 1964) and there is a discrepancy between the production of mucus and glycogen (Strauss, 1963). Dykova *et al.* (1963) found in 93 of 270 sterile women that during the last two days of the menstrual cycle the predecidual change of the stroma was deficient or lacking, and was associated with poorly developed blood vessels. In addition, Vaczy and Scipiades (1949) attributed importance to a decrease in the thickness and number of the collagen fibers as well as

to their disordered arrangement, since these investigators found such changes in 72.4 per cent of their sterile patients but in only 11.6 per cent of their controls. One should also remember that occasionally a luteinized cystic follicle developing after a failed ovulation can cause sterility with a secretory endometrium.

If amenorrhea exists then the endometrium usually is *hypoplastic* or *atrophic*. On the other hand, hypermenorrhea with *glandular-cystic hyperplasia* and a shift in the menstrual cycle can also prevent pregnancy. SILLO-SEIDL (1967) reported such a hyperplasia in 3.5 per cent of 467 curettages and endometrial biopsies from sterile patients. Even commoner is the *irregular proliferation* elicited by a persistent follicle of short duration. MASSHOFF (1941) referred to that proliferation as "glandular hyperplasia" and alleged it caused sterility in 24.5% of his patients. In our series (SILLO-SEIDL and DALLENBACH-HELLWEG, 1974) 28 per cent of 1915 sterility patients had *polyps;* 2 per cent were from the endocervix and 26 per cent from the corpus endometrium. 21 per cent of the patients became pregnant after the polyps had been removed by complete curettage.

In some countries, such as Spain, *tuberculous endometritis* is a major cause of sterility. In 3,000 curettings of sterile women BOTELLA-LLUSIA (1967) histologically found that 10.6 per cent had tuberculous endometritis. Signs of secretory changes were either deficient or lacking. In SILLO-SEIDL's series (Frankfurt, Germany) only 1.3 per cent among 467 of his sterile patients (1967) and only 0.7 per cent among 1 000 (1971) revealed tuberculous endometritis. SHARMAN in Glasgow (1955) reported the disease in 5.6 per cent of his patients, VACZY and SCIPIADES (1949, Budapest) in 7.1 per cent. In addition to the endometrial changes, the tuberculous salpingitis that exists concomitantly in most of these patients also causes sterility.

According to STEVENSON (1965), the patients with endometrial atrophy or hypoplasia have the least chance (20 per cent) of becoming pregnant after therapy, whereas women either with simple deviations in the length of the menstrual cycle or with deficient secretory phases have almost twice the chance (35 per cent).

g) Functional Disturbances During the Climacteric

At the end of the childbearing period ovarian function does not cease abruptly. Rather, the secretion of ovarian hormones wanes gradually over several years in a way unique in every woman. All variations in the balance of the hormones may develop from the gradual and concomitant waxing and waning of both ovarian hormones to an irregular overproduction or deficiency of one or both hormones, to a persistent secretion of only estrogen beyond the menopause (see Table 4). Accordingly, the histological picture of the climacteric endometrium varies greatly. Consequently, the spectrum of changes regarded as still physiological is much broader than that for the reproductive years (see p. 82ff). In addition, every investigator draws quite differently the boundaries separating the functional disturbances thought to be physiological from those clearly pathological. In our opinion a slight or even moderate functional variation in one or more menstrual cycles during the climacterium should not be judged as pathological.

Hence, irregular proliferative changes may be the result of an occasional anovulatory cycle, or irregular, usually inadequate secretory changes the result of an insufficient corpus luteum. Preferably, only those persistent changes that can be classified with a well-recognized clinical entity should be regarded as abnormal.

Of these entities the most common is *glandular-cystic hyperplasia.* It usually develops during the climacterium when the production of progesterone gradually ceases but that of estrogen continues. The condition is prognostically important and must be clinically followed. Depending upon the hormonal balance of the patient, glandular-cystic hyperplasia may either revert to a regressive hyperplasia or progress to an adenomatous hyperplasia. Similar considerations are valid for all other functional changes occurring during the climacterium, since it is impossible to predict at that time just how the changes will end; their development depends entirely upon what happens to ovarian function.

Much less common than the glandular-cystic hyperplasia is the socalled *secretory hypertrophy* of the climacterium. It probably is produced by overstimulation from excessive hypophyseal gonadotropin, which causes hyperactivity of a corpus luteum and extreme secretory changes in the endometrium (see p. 140f). The basalis, which normally is functionless, participates in the secretion. The changes that develop almost always disappear with the cessation of ovulation at menopause.

Polyps of the corpus endometrium (Lau and Stoll, 1962) are most frequent during the climacteric period. Their growth at that time is thought to be induced by the irregular stimulus of estrogen.

Most curettages performed during the climacteric period, however, reveal variations belonging within the broad spectrum of physiological changes expected at that time. The prognosis of these changes therefore is usually good, since they vanish as spontaneously as they appeared when the menopause sets in. Because the bleeding of these harmless cases cannot at times be distinguished from that of a more serious disturbance with dubious prognosis, a curettage during this critical period is indicated in every patient with bleeding. Carcinomas rarely develop at this time. In general they appear only after prolonged and total lack of progesterone.

h) The Effect of Hormone-Producing Ovarian Tumors on the Endometrium

The most common of these tumors are the estrogen-producing granulosa-cell tumors and the thecomas. A group of other tumors, especially the cystomas but metastatic tumors to the ovary as well, may by their growth and pressure stimulate the surrounding ovarian stroma to produce increased amounts of estrogen. In every instance the effect on the endometrium is the same: depending upon the amount of estrogen secreted, a glandular-cystic hyperplasia develops of variable intensity. If the production of estrogen is prolonged and unopposed the glandular-cystic hyperplasia becomes an adenomatous hyperplasia, which in turn may eventually develop into an adenocarcinoma. The changes produced are like those seen with a persistent follicle of long-standing.

In comparison, only a couple of types of tumors produce progesterone; they are also less common. The major examples are the luteoma and the partly luteinized

granulosa-cell tumors. They generally induce a high degree of secretory hypertrophy of the endometrium, with glands that secrete excessively and a stroma that often shows decidual change. Occasionally an estrogen effect is also evident. If such changes are seen in an endometrium of a postmenopausal patient then one should think first of an ovarian tumor. But in the differential diagnosis the possibility of previous therapy with gestagens must be considered, as for example that used in the conservative treatment of endometriosis.

In contrast, all other ovarian tumors that produce hormones, particularly the androgen-secreting androblastoma and the gynandroblastoma, are so rare that one seldom has the chance to study their effect on the endometrium. Clinically amenorrhea usually develops; the endometrium is hypoplastic or atrophic.

i) The Functional Disturbances of the Endocervical Mucosa

If a fractionated curettage has not been performed, then curettings of the endometrial cavity will often contain portions of the endocervix and transitional mucosa. Since the endocervix does not shed with menstruation, the functional disturbances induced in it by endogenous hormones are much less apparent than those seen in the endometrium. More important, however, is the fact that progesterone stimulates changes that are quite different from those produced by estrogen. The endocervical mucosa shows very little if any reaction to estrogen stimulation, but to elevated levels of progesterone reacts with *glandular and cystic hyperplasia,* as for example, with a persistent corpus luteum, or with pregnancy. The height of the endocervical mucosa increases and its surface often becomes papillary. Its glands either grow, branching excessively, or dilate cystically, filling with mucus. Reserve-cells of both the surface epithelium and the glands may proliferate intensely ("reserve-cell hyperplasia").—The transitional mucosa may show cystically dilated glands from the stimulation by both hormones; it represents a continuation of the hyperplasia of the endometrium and endocervix. Glandular-cystic hyperplasia of the cervical or transitional mucosa is of little clinical importance, since it is not desquamated and rarely causes bleeding. The excessive mucus secreted by the cystically dilated glands may occlude the endocervical canal or result in an annoying vaginal discharge.

3. Endometritis

The histologic concept of endometritis has changed considerably since the turn of the century. With the increase in our knowledge of the normal histology of the endometrium during the last decades, the concept has narrowed. Before HITSCHMANN and ADLER (1907, 1908) discovered the histological changes of the menstrual cycle, the physiological secretory phase was regarded as an "endometritis glandularis hypertrophica". In like manner, RUGE (1880, see RUCK, 1952) distinguished glandular endometritis from interstitial endometritis. In the decades that followed glandular-cystic hyperplasia was viewed as a hypertrophic, hyperplastic, or polypoid endometritis. There were two reasons for that: first, because in their searches for a lesion to explain the discharge in their patients,

investigators often found a hyperplastic endometrium; second, because the hyperplastic endometria usually showed hemorrhagic necroses (see for example, R. MEYER, 1923). It was only after glandular-cystic hyperplasia was associated with an elevated level of estrogen that the cause and effect of the entity became understood (SCHRÖDER, 1928). RUCK's (1952) historical review offers detailed information on this subject. Until recently it was commonly believed that in the second half of the normal secretory phase polymorphonuclear leukocytes infiltrated the compacta of the endometrium, although an explanation for the unusual, presumed infiltration could never be stated. When accumulations of the leukocyte-like cells were encountered they were thought to indicate an endometritis. Such an endometritis, however, has disappeared from our catalogue of diagnoses, since we now know that these leukocyte-like cells are differentiated stromal cells (endometrial granulocytes), which have nothing to do with inflammation. The endometrial granulocyte is a normal component and product of the endometrial stroma (HAMPERL, 1954; HELLWEG, 1954). Similarly, the presence of lymphoid follicles in the endometrial stroma cannot be interpreted as evidence of an endometritis (for literature see RUCK, 1952; RAHN, 1968; see p. 30f). Thus, the more we have learned about the histology of the endometrium the more we have had to reclassify conditions previously thought to be pathological as physiological or functional variations of the normal menstrual cycle.

In separating a true endometritis from apparent inflammatory changes, it is necessary therefore to apply strict criteria. Such may be as clearly specified for the acute endometritis as for the chronic form; they correspond to the criteria ascribed inflammatory reactions seen in other tissues and organs. Since the processes of inflammation chiefly involve the connective tissues and blood vessels, the inflammatory reaction in the endometrium takes place primarily in the stroma. An infiltrate of inflammatory cells is needed to make a diagnosis of endometritis. When strict standards are applied, endometritis is far less common than previously assumed. After excluding all post-abortion and postpuerperal endometria, RUCK (1952) diagnosed endometritis seventy times in 2,759 curettings; that is, in 2.6 per cent of the curettings. Women in the second half of the childbearing period more often had endometritis than did the younger (see also WINTER, 1956).

a) Acute Endometritis

is most commonly associated with an intrauterine abortion, which can be recognized by demonstrating the remnants of placenta and decidua. (Abortions are discussed more fully on p. 259ff.) Further causes of acute endometritis are microorganisms, as well as physical, chemical and thermal agents. Examples of some of these are: foreign bodies inserted into the uterine cavity (intrauterine devices, talcum crystals, fragments of tampons) or necrotic remnants of tissue acting as foreign matter (twisted polyps, necrotic portions of leiomyomata, or cartilaginous and bony residua of a dead fetus). Besides the primary cause, which may either reach the uterine cavity from outside (for example, bacteria) or develop within the cavity (for example, sloughed remnants of necrotic tissue), a secondary cause, a wound of the endometrial lining, is necessary for the inflammation to become established. Such a wound occurs at every menstrual period, every

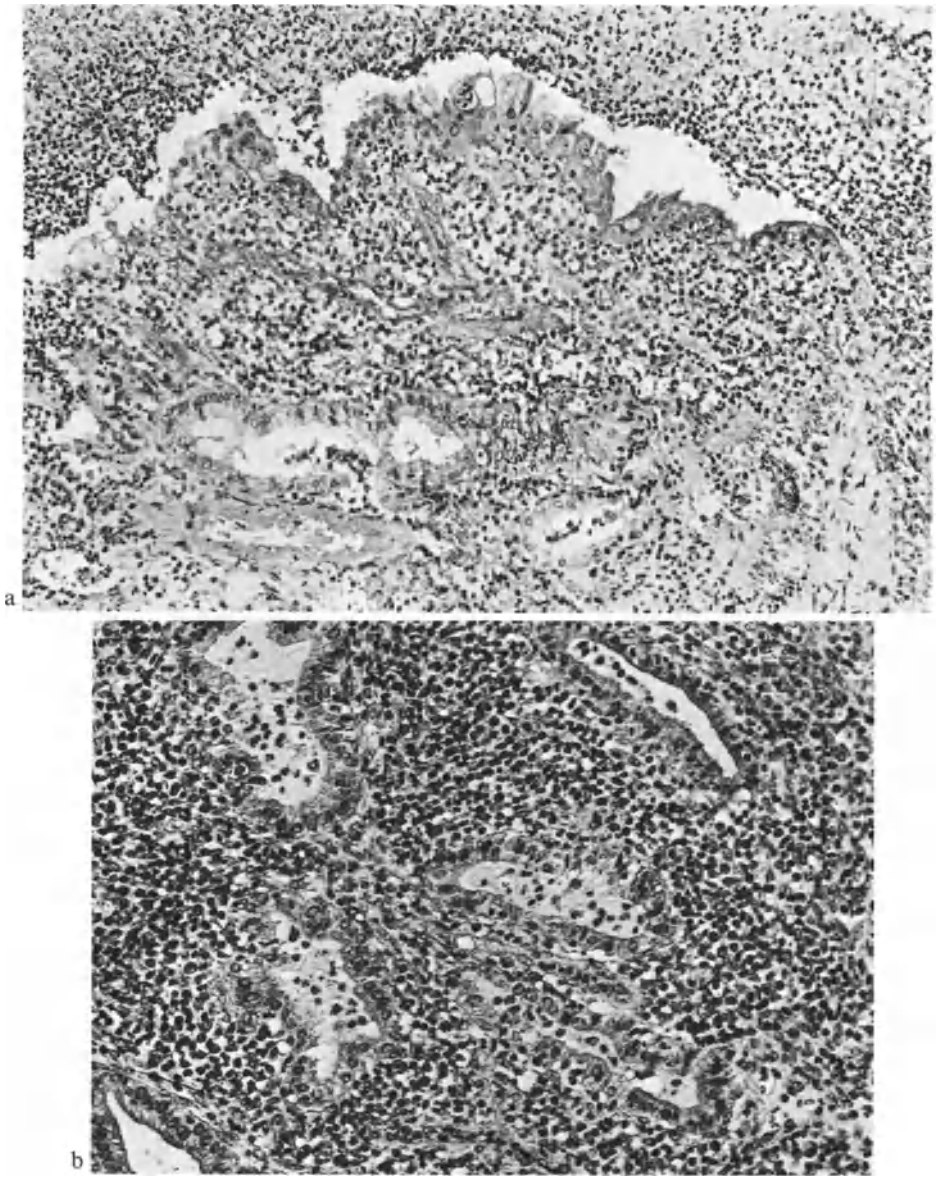


Fig. 74a and b. Acute endometritis. The stroma is diffusely and densely infiltrated with polymorphonuclear leukocytes. Glandular epithelium is destroyed (a) and glandular lumina contain leukocytes (b)

abortion and every pregnancy, and is induced with every curettage. In all these conditions the cervical os is dilated, facilitating the ascent of bacteria into the uterine cavity (HOMMA, 1955). Consequently, it is during these conditions when an acute endometritis usually develops.

Although the noxious agents causing acute endometritis vary greatly, the inflammatory reaction to them all is generally the same. *Histologically,* we find

in the stroma heavy, focal infiltrates of polymorphonuclear leukocytes, which we can readily distinguish from the endometrial granulocytes since they penetrate and destroy the glandular epithelium and fill the glandular lumina (Fig. 74). The tissue at the leukocytic infiltrates undergoes dissolution and becomes necrotic, and the reticulum fibers disintegrate. The stroma about the infiltrates becomes variably hyperemic, edematous and hemorrhagic, in no way related, however, to the phase of the menstrual cycle. The reticulum fibers elsewhere remain intact (SEKIBA, 1924). The hormonally-induced changes that take place in the glands and stroma during the menstrual cycle need not be affected, and with the next menstruation the inflamed functionalis can be shed. In that way an acute, localized inflammation limited to the superficial endometrium may be discharged and the region heal. Often, however, the basal layers of the endometrium are involved, so that with the regeneration of the endometrium from below the inflammatory process again reaches the surface. In addition to the typical inflammatory changes of the endometrium described here, further changes may develop like those seen in other tissues. These changes (for example, edema, exudation, hemorrhage) cannot be regarded as characteristic of endometritis, since they may also be brought about by the physiological or pathological stimulation of hormones. A diagnosis of an endometritis can be made with assurance only if one limits oneself to those morphological criteria that are not induced by hormones.

b) Chronic Nonspecific Endometritis

develops in a woman who is still having menstrual periods only when the inflammation persists in the basalis or other parts that are not shed. The noxious agents causing chronic endometritis are the same as those that induce acute endometritis. CADENA *et al.* (1973) reported that in the 152 women they studied with endometritis chronic inflammation was nonspecific in 84 per cent. Of these, it was caused by remnants of abortion in 41 per cent, by postpartum factors in 12 per cent, by intrauterine contraceptive devices in 14 per cent, and by pelvic inflammatory disease in 25 per cent. Primary chronic endometritis, however, develops only after the menopause, when the inflammatory process can persist and spread throughout the non-shedding endometrium.

Histologically, the infiltrates of plasma cells and lymphocytes are characteristic, particularly the plasma cells, which can readily be detected with the methyl green-pyronine stain because it colors their abundant cytoplasmic RNA a bright red. Both types of cells are either scattered diffusely throughout the stroma or aggregated focally. Like the polymorphonuclear leukocytes, they can infiltrate and destroy the glandular epithelium (Fig.75). They may also accumulate in the glandular lumina but do so less often than the polymorphonuclear leukocytes. In addition, a destruction of tissue is much less common. Often the endometrial architecture is so well preserved that under low magnification the infiltrates of chronic inflammatory cells may barely be evident. In contrast, the hormonally-induced cyclic changes of the endometrium are usually profoundly affected, depending however on the severity of the inflammation. The postmenstrual epithelialization of the denuded endometrium is severely delayed at times and the regeneration of the endometrium greatly prolonged. If the secretory phase devel-

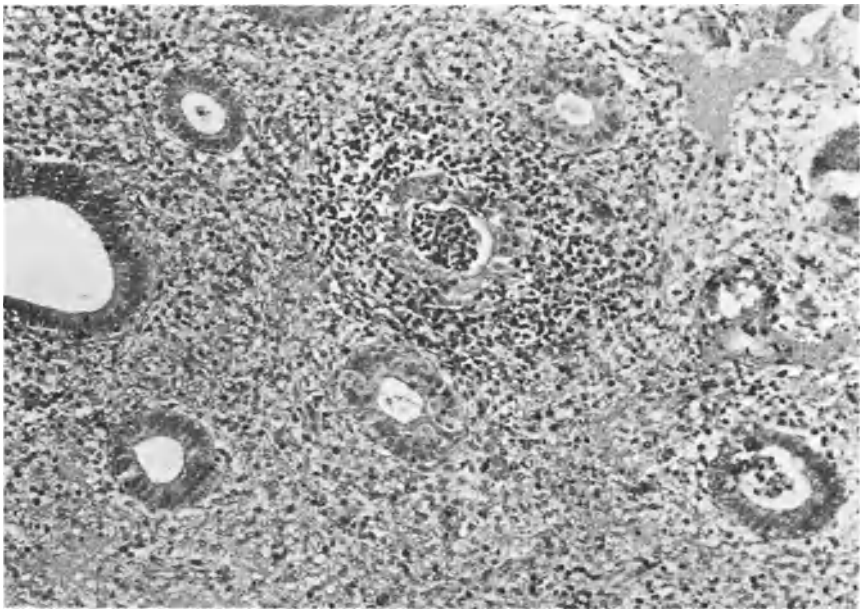


Fig. 75. Chronic endometritis. Lymphocytes and plasma cells have focally infiltrated the stroma and penetrated the glandular epithelium which is disintegrating

ops at all, it is deficient. Often the endometrium either remains in the proliferative phase or becomes afunctional. On light- and electron-microscopic studies, chronic productive changes in the connective tissue or in the blood vessels are seldom seen, since these structures in the endometrium are almost exclusively under hormonal control. It is exactly this responsiveness of the endometrium to hormones, however, that is affected by the chronic inflammation. Previously it was assumed that the chronic inflammation stimulated the glands to proliferate; the assumption has proved wrong. Instead, the epithelial cells undergo secondary degenerative changes; at first they swell, then they become necrotic and desquamate. After prolonged inflammation the endometrium fails to proliferate, reaching a histological state known as "endometritis atrophicans".

Senile endometritis is almost always associated with an atrophic endometrium, the relationship being like that between senile vaginitis and atrophic vaginal mucosa. Since senile endometritis may cause postmenopausal bleeding, it necessitates histological study to rule out a carcinoma. We usually find that the atrophic endometrium is diffusely infiltrated with lymphocytes and plasma cells; its surface may be ulcerated. Often the defect becomes covered with a metaplastic, squamous epithelium. In extreme cases when the entire uterine cavity becomes lined by such a squamous epithelium, the condition is referred to as "ichthyosis uteri". Although it presents a startling picture, it is neither precancerous or cancerous and persists as a benign metaplasia. It must, however, be differentiated from the squamous epithelial components of an adenoacanthoma.

If the endocervical canal or cervical os become stenosed (e.g., by a carcinoma or from scarring after insertion of radium or after cryosurgery or amputation

of the cervix), then the inflammatory exudate cannot be discharged; it accumulates and a *pyometra* develops.

Before one finally decides to make the diagnosis of "non-specific endometritis" one should attempt to find the cause, which may be present as necrotic tissue or as a foreign body in an isolated fragment of the curettings. In any case, a search must be made for products of conception in suspected abortion, especially when the endometrium is undergoing a delayed involution.

c) Tuberculous Endometritis

in Germany has become uncommon, in the United States extremely rare (ISRAEL *et al.*, 1963). In some European countries, however (Spain: BOTELLA-LLUSIA, 1967; Hungary: VACZY and SCIPIADES, 1949; England: SUTHERLAND, 1958), it is more common, and in India quite frequent (MANNDRUZZATO, 1964). It is almost always associated with a tuberculous salpingitis, from which the bacteria descend to infect the endometrium. The denuded surface of the postmenstrual endometrium is especially susceptible to infection by the bacteria in the tubal secretions. The uterus is involved in about 49 per cent of the cases of genital tuberculosis (THOM, 1952). Endometrial involvement is most frequent during the third to fourth decade; it may also occur, although rarely, in the postmenopause (HASSELGREN and BOLIN, 1977). A socalled primary infection of the endometrium, which is produced by hematogenous spread from a pulmonary focus, is exceedingly rare. A latent, chronic tuberculous endometritis may acutely exacerbate after a pregnancy (MEINRENKEN, 1949). Occasionally it is possible to demonstrate the bacteria in the endometrium with the fluorescent microscope (FINKE, 1950) but rarely with bacteriological methods (ERIKSEN, 1947). Generally, however, neither fluorescent microscopy nor the cultural techniques prove successful, thus the diagnosis must rest entirely on the histological diagnosis of the biopsy specimen.

The extent of the tuberculous inflammation in the endometrium may vary profoundly. As in nonspecific, chronic endometritis, the most prominent features may be the diffuse or focal infiltrates of lymphocytes and plasma cells in the stroma with involvement and destruction of the glands. These may be the only changes seen in latent or treated tuberculosis. Often in such instances the tuberculous etiology of the chronic endometritis first becomes evident only after the fallopian tubes are removed and found to be involved by a typical caseating tuberculosis. Occasionally the endometrial infiltrates contain typical granulomata with variable numbers of epithelioid cells and a few Langhans giant cells, all surrounded by a dense zone of lymphocytes. Under low magnification these granulomata can be detected in the densely cellular stroma as pale staining, indistinct, rounded lesions, the socalled microscopic tubercle. Frequently such lesions erode through the epithelium of a neighboring gland and fill its lumen (Figs. 76 and 77). The adjacent intact epithelial cells often respond by atypical proliferation, showing irregular stratification and metaplasia; some cells may contain prominent vacuoles of mucus (SCHRÖDER, 1920). At times the stromal cells also become hyperplastic and decidual-like, a change perhaps representing a widespread transformation into epithelioid cells (ZANDER, 1949). In severe

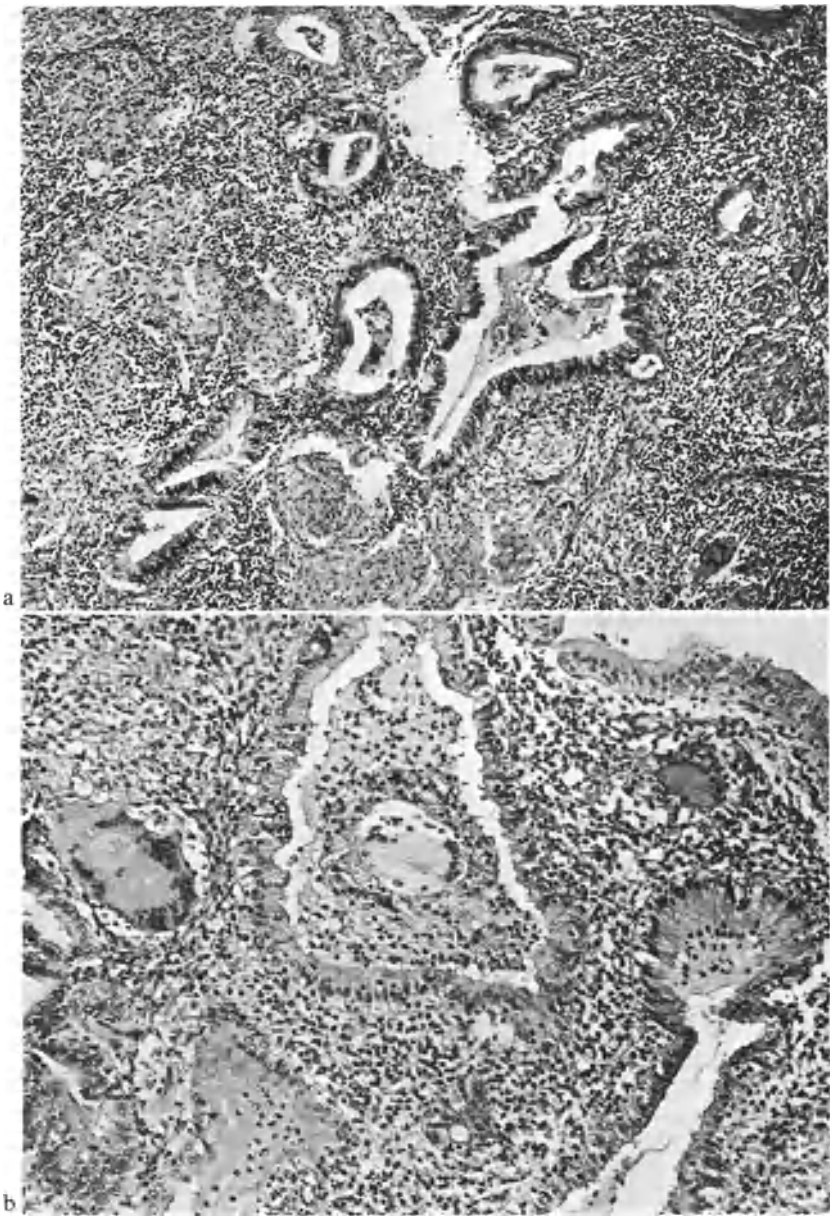


Fig. 76a and b. Tuberculous endometritis. A tubercle, comprised of compact epithelioid cells and Langhans giant cells, breaks through into the glandular lumen. (a) Low magnification. (b) Higher magnification

infections the endometrial surface may ulcerate or undergo extensive caseation necrosis. If the endocervical canal becomes blocked, preventing discharge of the inflammatory exudate, a pyometra results. A curettage under such conditions may cause miliary dissemination of the infection (BÜNGELER, 1935). In 20 per

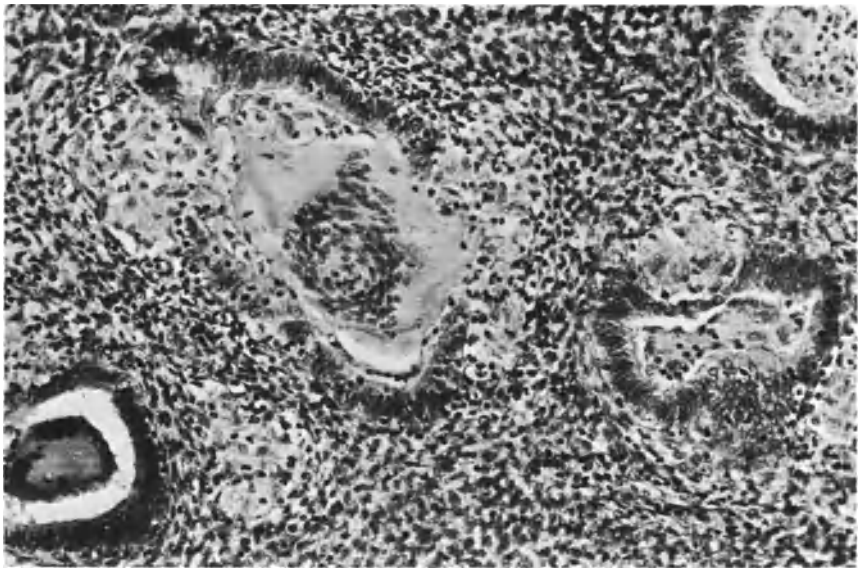


Fig. 77. A tubercle containing large Langhans giant cells breaks into a glandular lumen

cent of their cases of tuberculous endometritis. NOGALES *et al.* (1966) found involvement of the basalis. Only in the severest cases does the infection spread to the myometrium (DE BRUX and DUPRÉ-FROMENT, 1965). At the other extreme, if only a few tubercles exist and are localized to a small fragment of the curettings not included in the plane of section, then the tuberculous endometritis will go undiagnosed. When tuberculosis is suspected clinically or when a chronic endometritis exists without evident cause, then the paraffin block should be sectioned at deeper levels and a search made of all tissue fragments for a possible tuberculous granuloma. It is obvious why a simple strip biopsy is unsuitable for diagnostic purposes in these cases.

Often the tuberculous infection greatly suppresses the sensitivity of the endometrium to ovarian hormones. Sterility, which is primary in 94% and secondary in 6%, almost always results (SILLO-SEIDL, 1967; NOGALES-ORTIZ *et al.,* 1979) from either the functionally altered endometrium or the associated tuberculous salpingitis. The endometrium is often functionally inert or monophasic, although it may exhibit a deficient secretory phase with a defective secretion of glycogen and an irregular distribution of glycogen and mucopolysaccharides. The stroma may however appear almost normal. As the literature indicates, the incidence of a co-existing glandular-cystic hyperplasia varies greatly (NOGALES *et al.,* 1966: 1.1 per cent; KIRCHHOFF, 1955: 1.4 per cent; BEHRENS, 1956: 6 per cent; NEVINNY-STICKEL, 1952: 24 per cent; STÜPER, 1955: 30 per cent; SCHAEFER *et al.,* 1972: in all of their postmenopausal cases). The fibrosis about the tubercles, nevertheless, inhibits endometrial shedding during menstruation (NEVINNY-STICKEL, 1952). Since a tubercle requires about fifteen days to develop and tubercles are frequently found in the early proliferative phase, it is evident in such instances that at least those regions with tubercles could not have been discharged during

menstruation. Most likely the involved regions remain for several cycles (NOGALES *et al.*, 1966). Supporting that opinion is the rare discovery that a polyp may contain tubercles but the remaining endometrium is free of tuberculosis. The proliferating endometrium becomes re-infected either from persisting foci or from recontamination of the surface by infectious discharges from the fallopian tubes.

Sterility may be the only clinical symptom of tuberculous endometritis. Not infrequently tuberculous endometritis is incidentally found at autopsy (THOM, 1952); occasionally the diagnosis made from curettings comes as a surprise for the gynecologist.

If fertilization takes place, the blastocyst usually implants in the fallopian tube. According to DE BRUX and DUPRÉ-FROMENT (1965), 5 per cent of all extrauterine pregnancies are caused by a chronic or healing tuberculous salpingitis. If, however, intrauterine implantation does occur, then the mother (WALTHARD, 1933; MEINRENKEN, 1949) or the child (KAPLAN *et al.*, 1960) may die after delivery or after induced abortion from a miliary tuberculosis.

Tuberculous endometritis may be cured with specific therapy. The tubercles heal as hyalinized fibrous tissue and scars; the infiltrates of chronic inflammatory cells, however, persist in the endometrium for years.

d) Specific Endometritis Caused by Rare Microorganisms

Cryptococcus glabratus, an asporogenous budding yeast, may in rare instances produce a granulomatous endometritis that closely resembles tuberculosis (PLAUT, 1950). Generally the organism, a normal inhabitant of soil, may be found as a saprophyte in feces, urine and sputum. Equally as uncommon is the granulomatous endometritis caused by *Blastomyces dermatitidis* (FARBER *et al.*, 1968). Blastomycosis often looks so much like tuberculosis histologically that in order to find and identify the fungal organisms special stains are needed; among these the Gridley stain (see HUMASON, 1962), the PAS reaction, and the Gomori silver-methenamine stain are especially valuable. A granulomatous endometritis also closely resembling tuberculosis may be caused by infection with *T-Mycoplasma*. Although it usually produces few local signs or symptoms, this infection was reportedly associated with infertility or repeated spontaneous abortions (HORNE *et al.*, 1973).

Sarcoidosis of the endometrium, although rarely reported in the literature, may not be as rare as it seems (TAYLOR, 1960). Spread by ascending reflux may occur, especially after an intrauterine abortion (BURKMAN *et al.*, 1976). Because sarcoid granulomata so closely resemble those of tuberculosis, it seems likely sarcoidosis is not infrequently misdiagnosed as tuberculosis. All attempts should be made to distinguish it from tuberculosis, however, since therapy and prognosis for the two diseases are different (see Fig. 78). If the detection of acid-fast bacteria fails, then slight or absent necrosis in the granulomata of the fallopian tubes strongly suggests sarcoidosis (CHALVARDJIAN, 1978).

Gonorrheal endometritis is the result of an ascending infection from the cervix and represents a transitional stage in the development of gonorrheal salpingitis. Histologically it appears as a nonspecific chronic endometritis with especially

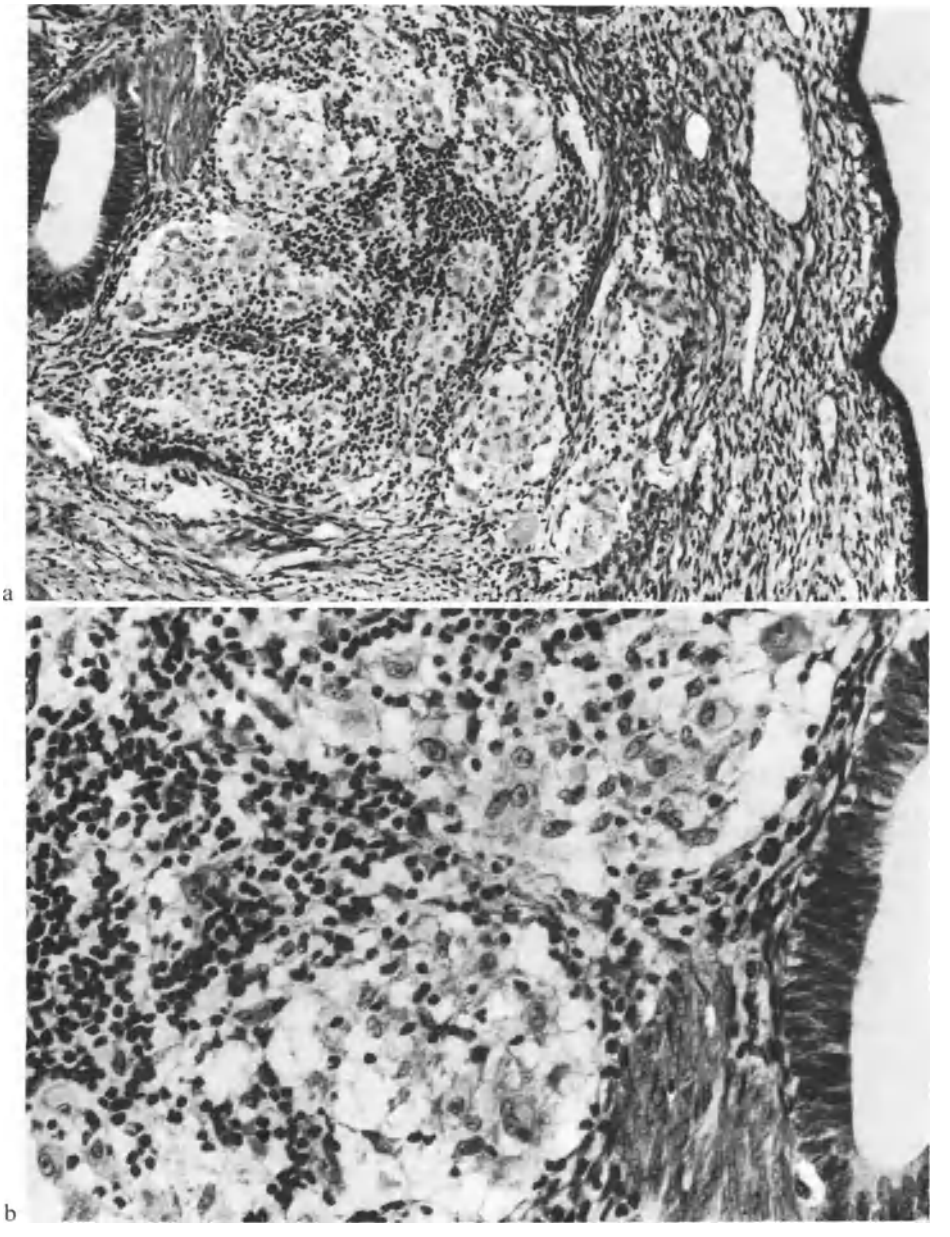


Fig. 78a and b. Sarcoidosis of the endometrium. Epithelioid-cell granulomata without evidence of necrosis. (a) Low magnification. (b) Higher magnification

dense inflammatory infiltrates. The abundance of plasma cells is characteristic, but eosinophils often may also be unusually numerous. Reactive hyperplasia of the endometrial glands often ensues. The inflammation may spread to involve the myometrium.

A hematogenous infection of the endometrium by *pneumococci*, although extremely rare, may develop especially postpartum as a complication of lobar pneumonia (NUCKOLS and HERTIG, 1938; MCCARTHY and CHO, 1979).

Toxoplasmosis of the endometrium is thought by some investigators to be more common than previously believed, yet one authority (PIEKARSKI, 1970) doubts whether the entity really exists. WERNER *et al.* (1968), with the aid of the immunfluorescent method, reported detecting trophozoites in endometria and in smears of menstrual blood from patients with latent infection. Endometrial toxoplasmosis allegedly is the cause for congenital toxoplasmosis and for some habitual abortions (LANGER, 1963, 1966), though proof of that contention is still lacking. Of 172 patients with abortions, toxoplasma were identified in only one by means of inoculation studies in animals (JANSSEN *et al.*, 1970). Histologically, the organism was seen also only once among 87 patients with abortions (KRÄUBIG, 1972). Supposedly the infection develops as follows: the parasites reach the uterus by way of the blood stream (parasitemia), entering the basalis either directly or after invading from the myometrium. In the basalis the toxoplasma encyst. As the endometrium proliferates the pseudocysts are carried upwards into the functionalis. With menstruation the cyst wall may rupture, liberating the proliferating forms into the endometrial cavity, whence they may again invade the endometrium and form new pseudocysts in the basalis (WERNER *et al.*, 1968). If toxoplasma do infect the endometrium as just outlined, it is strange that the histopathology of the infection has never been identified and reported.

Schistosomiasis of the endometrium is endemic in the Far East, Africa, and Central America, but it may be found in the temperate zone in a patient who once had lived in any of these tropical regions (BERRY, 1966). Diagnosis of the endometrial infestation is usually made by demonstrating the ova of the Schistosoma haematobium or mansoni in smears of vaginal or cervical secretions. The ova may also be found histologically in the endometrium or in the subepithelial stroma of the cervix. Here they induce either no reaction, or a decidual-like change in the surrounding stroma (WILLIAMS, 1967), or a granulomatous inflammation resembling a tubercle, or a diffuse infiltration of eosinophils, histiocytes, lymphocytes, and plasma cells. The mucosal surface may ulcerate. Papillomatous growths may develop on the portio vaginalis (ectocervix). In rare instances the endometrium may be destroyed and replaced by a hemorrhagic granulation tissue. The patients are amenorrheic and sterile (MOUKTHAR, 1966).

Actinomycosis of the endometrium is extremely rare. The actinomyces infect the endometrium by way of the vagina or by hematogenous dissemination from a focus elsewhere, e.g., an actinomycosis of the appendix (MACCARTHY, 1955). The uterus may become a sac of granulation tissue filled with pus in which countless granules of actinomyces are found (HÜFFER, 1922; for additional references see BLOCH, 1931). LOMAX *et al.* (1976) reported actinomycotic endometritis developing after insertion of intrauterine devices. A mycotic endometritis consistent with *Candida* infection was observed in a 38 year old female after prolonged therapy with progesterone (RODRIGUEZ *et al.*, 1972). Endometrial coccidioidomycosis developed in a patient with a disseminated infection (CHUAN *et al.*, 1975). An infection of the endometrium with *Herpes virus* has been described in a

29 year old patient following an abortion. The enlarged opaque nuclei of the glandular epithelial cells contained prominent rod-shaped inclusions, and chronic inflammatory cells infiltrated the endometrial stroma (GOLDMAN, 1970). The report raises the question whether herpetic endometritis may be the cause of neonatal herpetic infection. Recently MCCRACKEN *et al.* (1974) and DEHNER and ASKIN (1975) published similar cases of spontaneous abortion due to *Cytomegalovirus endometritis* in which the endometrial glandular cells bore characteristic large inclusions.

Malakoplakia of the endometrium (THOMAS *et al.,* 1978) was the cause of postmenopausal bleeding in his patient. The histological and electron microscopic studies of the granulomatous endometritis revealed the typical Michaelis-Gutmann bodies and the rod-shaped bacteria in abnormal histiocytes.

In 1960 PERKINS described a case of *"pneumopolycystic endometritis"* in which vesicles of gas, closely resembling those seen in colpitis emphysematosa, had formed in the endometrium. He believed the vesicles were the result of an infection with gas-forming bacteria.

e) The Foreign Body Granuloma

Various substances are capable of eliciting in the endometrium a foreign body reaction, which histologically resembles that seen in other tissues.

In those countries where *talcum powder* is still used, talcum granulomata may develop after intrauterine procedures. The particles of talc get carried into the endometrial cavity either by curettes or by probes (HAUDE, 1956), which are contaminated with surgical dusting powder, or by the insertion of sulfonamide-containing suppositories in which talcum powder serves as a binding agent (BECKER, 1950; MARTIN, 1951; STRAKOSCH and WURM, 1951; SCHUMACHER, 1956; KNORR, 1960). When the talc particles become embedded in the endometrial stroma, usually that of the basalis, they elicit a chronic inflammatory reaction of the granulomatous type. Histiocytes infiltrate to surround the particles of talc, and the multinucleated giant cells that subsequently form from them attempt to phagocytize the particles (Fig. 79). Vessels nearby proliferate; lymphocytes and plasma cells infiltrate the region. Depending upon the number and size of the talc particles and upon the extent of the inflammatory reaction induced, a chronic endometritis of variable intensity results. When it is severe, focal necroses may result and the granulomata may even erode into the myometrium. In hematoxylin-eosin stained sections the talc crystals are easily recognized as refractile, glass-like splinters or fragments. If torn away from the tissue during sectioning, the angular empty spaces they leave behind in the granulomata serve as important clues. Because the crystals are birefringent they can be readily distinguished from other foreign matter with the polarizing microscope. Talc crystals (hydrous magnesium tetrasilicate) however resemble crystals of sulfonamide, which are also birefringent. The talc crystals, unlike the sulfonamides, are resistant to dilute hydrochloric acid and heat. Talc particles may remain in the uterine tissues for years, and if scanty, may produce no clinical symptoms. When the granulomata are large and numerous, however, the regeneration of the endometrium after menstruation may be disturbed either physically or chemically (through the lib-

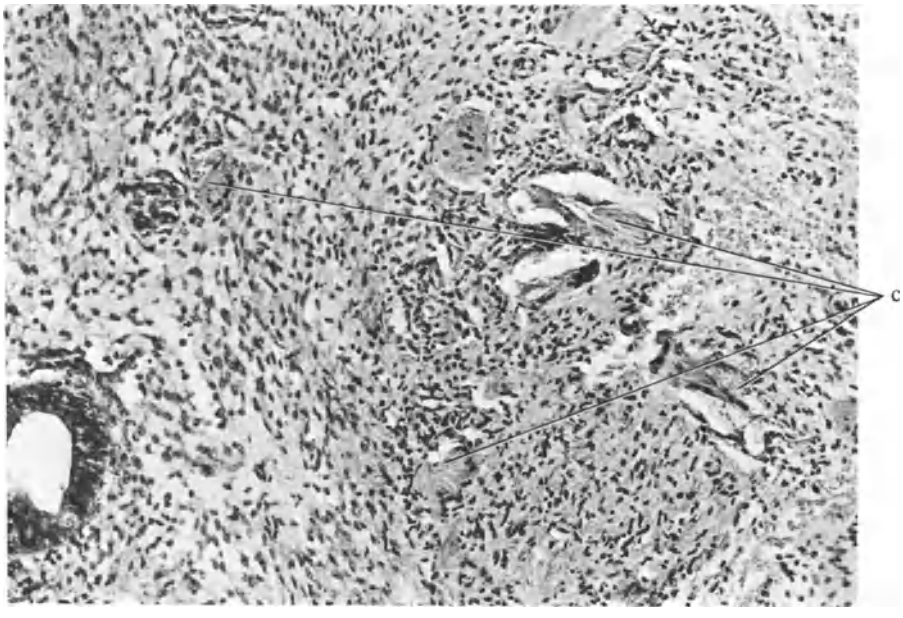


Fig. 79. Talcum granuloma. Needle-like and fan-shaped talc crystals (c) in the stroma are surrounded by foreign body giant cells and lymphocytic infiltrates

eration of silicic acid). Menorrhagia or a discharge may ensue (SCHUMACHER, 1956). In the differential diagnosis all other types of endometritis should be considered, especially tuberculous endometritis and postabortal endometritis. The talc crystals must be identified before the diagnosis of talc granuloma is made.

An *intrauterine contraceptive device*, a foreign body in the true sense of the word, induces in some patients (according to JESSEN *et al.*, 1963, in 10.1 per cent) an acute or chronic endometritis of variable intensity. Where the device contacts the endometrium it may destroy the superficial epithelium. The surrounding stroma may become densely infiltrated with polymorphonuclear leukocytes, lymphocytes and plasma cells (see p. 248). The formation of foreign body giant cells about the devices occurs only rarely, probably because they are made of relatively innocuous material. The rather high incidence of endometritis induced by the older types of intrauterine devices was primarily related to their purely mechanical effect, which depended on shape, size, and chemical composition. In contrast, the modern copper T-devices or those containing gestagens injure a normal endometrium only rarely, leading at most to a light infiltration of polymorphonuclear leukocytes within the superficial spongiosa and the lumina of the glands. It is primarily when the endometrium is severely underdeveloped that a focal endometritis develops.

Intrauterine instillation (e.g., of a liquid tissue-adhesive to control profuse bleeding or to cause permanent sterility) may also be accompanied by acute or chronic endometritis (c.f. p. 254).

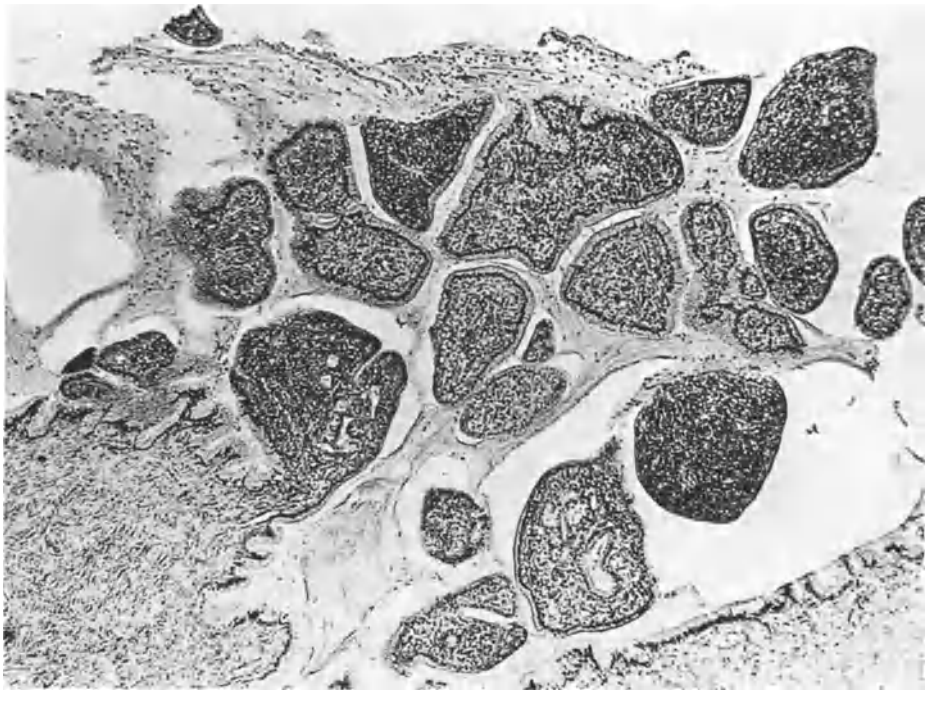


Fig. 80. Chronic endocervicitis. Lymphocytes densely infiltrate mucosal papillae

f) Endocervicitis

(endometritis cervicalis). Just as disease may be limited to the endometrium, so may an inflammation involve only the endocervix, ending often at the internal uterine os. The endocervicitis usually follows an infection that ascends from the portio vaginalis. Acute and chronic nonspecific inflammation is common and develops after an inflammatory erosion of the portio or after an eversion of the endocervical epithelium. (Specific inflammations are much rarer.) Histologically the mucosa is papillary, edematous and densely crowded with polymorphonuclear leukocytes, lymphocytes and plasma cells (Fig. 80). Often the superficial columnar epithelium is replaced by metaplastic squamous epithelium. A gonorrheal infection causes a severe inflammation more often in the endocervix than in the endometrium. The frequency and histology of tuberculous endocervicitis correspond to those of tuberculous endometritis.

4. Neoplasms

a) Benign Tumors

In our experience benign neoplasms of the endometrium are very rare, primarily because we consider most **benign epithelial growths** of the endometrium (e.g.,

the polyps) as localized hyperplasias and not as true tumors (see p. 123 ff). The etiology and morphology of these epithelial growths require that they be classified in the broad spectrum of polypoid glandular-cystic and adenomatous hyperplasias. The old expression "adenoma of the endometrium" has given way to the modern term "adenomatous polyp". The papillomas of the endometrium described in former times actually were exophytic, papillary carcinomas. There is no such tumor as an endometrial papilloma.

Since they originate from the endometrial stroma, the **benign growths of the connective tissues** also represent stromal hyperplasias in most instances. Sarcomas may arise directly from them without benign tumors developing as transitional stages. In searching the literature we found only one description of an "endometrial stromaloma" (ROSENBERG *et al.*, 1964). Although this tumor grew so large and polypoid that it filled the uterine cavity, it remained nonetheless localized to the endometrium. Histologically, it consisted of uniform stromal cells enmeshed in reticulum fibers. There was no evidence of invasive growth or malignancy. Since the myometrium was not invaded, the tumor cannot in my opinion be properly classified with stromal endometriosis.

Hemangiomas of the endometrium and myometrium have been diagnosed from time to time (R. MEYER, 1925; NEUMANN, 1929; MARSH, 1950; GRUND and SIEGEL, 1954; HUNTER and COGGINS, 1965). Grossly, these tumors resemble hemorrhagic polyps. Histologically, they usually arise from the inner myometrium and either grow into the endometrium or push it away. The endometrial stroma contains innumerable large and small, thin-walled blood vessels. One patient reported also had multiple cutaneous hemangiomata.

IRWIN (1956) described a primary *lymphoma* of the endometrium, which was polypoid and composed of many closely packed lymphoid follicles with prominent germinal centers. A few scattered endometrial glands could still be found within the tumor. SCHINKELE (1947) reported an *angiomyoma* of the functional layer of a secretory endometrium. Presumably the tumor had originated from smooth muscle cells of a blood vessel. Grossly the tumor appeared as a red nodule within the endometrium. HOLZNER and LASSMANN (1967) diagnosed as *"neurofibromatosis"* of the endometrium circumscribed, fasciculated proliferations of Schwann cells that extended to just beneath the superficial epithelium. Similar proliferations were evident as well in the myometrium.

A rare benign variant of the malignant mixed Müllerian tumor is the papillary *cystadenofibroma* of the endometrium (VELLIOS and REAGAN, 1973). This is usually found as an irregularly knobby or richly polypoid growth protruding into and filling the uterine cavity. Its elongated polyps are composed of closely crowded, spindle-shaped fibroblasts and are covered with an epithelium of cuboidal or columnar cells that may secrete mucus or show squamous metaplasia like that of the endocervix. Owing to the inherent growth potentialities of the epithelium and the profuse branchings of the polyps, buds of epithelium become caught up in the cellular stroma to form gland-like structures. The tumor resembles an ovarian adenofibroma. It must be distinguished from a well-differentiated homologous stromal sarcoma, which generally is not papillary, is better vascularized, and whose stromal cells often show mitoses (GRIMALT *et al.*, 1975).

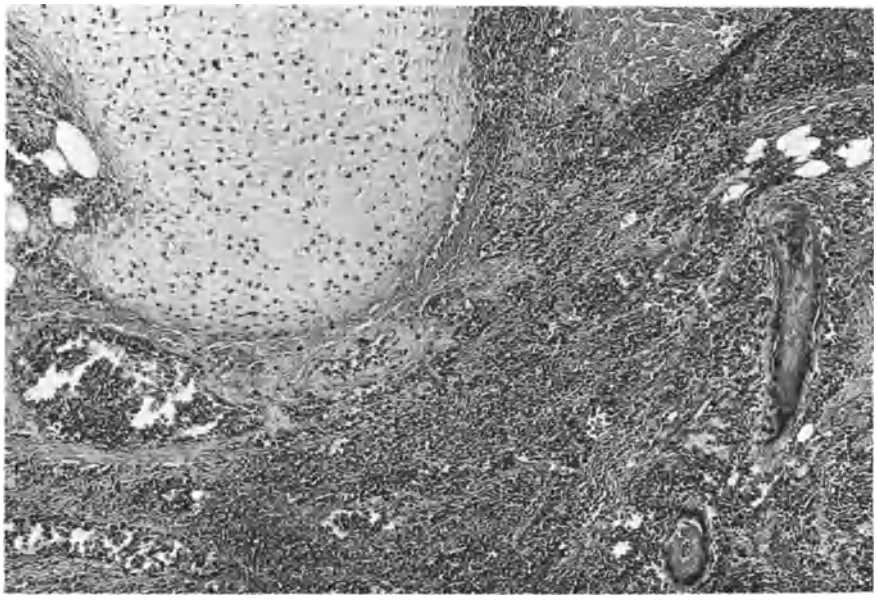


Fig. 81. Teratoma of the endometrium. Nodule of immature cartilage at upper left bounded by numerous blood-filled vessels and large infiltrates of lymphocytes. At upper right cross-sectioned skeletal muscle and a few vacuoles of fat; at lower right abnormally developed hair follicles

Recently we have seen a peanut-sized lesion of the endometrium that we diagnosed as a *benign solid teratoma* (DALLENBACH-HELLWEG and WITTLINGER, 1976). It consisted of peculiarly shaped portions of normal appearing embryonal cartilage, thick-walled and tortuous vessels, twisted bundles of nerves, ducts of respiratory and intestinal epithelium, and sheets of skin, all of which were so scrambled together as to convince us the lesion was not the remnant of a malformed embryo (Fig. 81). In addition, we could find no traces of placental or decidual tissue in the surrounding endometrial tissues. MARTIN *et al.* (1979) reported on a benign cystic teratoma of the endometrium and suggested it may have arisen from an injured fertilized ovum or one that underwent parthenogenesis.

b) Carcinoma of the Endometrium

The statistics in the literature on the **frequency** of endometrial carcinoma vary considerably. In general, however, the tumor has increased during the last few years as compared with carcinoma of the cervix. Forty years ago the ratio of endometrial carcinoma to cervical carcinoma was 1:14.8 (HINSELMANN, 1930), and ten to twenty years ago it was 1:3 to 4. Nowadays, however, in the larger gynecological hospitals endometrial carcinoma is diagnosed as often as cervical carcinoma (GORE and HERTIG, 1962; WYNDER *et al.*, 1966; HELD, 1969). The increase in the incidence of endometrial carcinoma is surely not just because women are living longer; there are other significant reasons but these will be discussed later. It should be mentioned now, however, that the relationship of endometrial carcinoma to cervical carcinoma is also racially dependent. For example, in Jewish women in New York City the ratio of these two carcinomas

is 1:0.3 (they rarely develop cervical carcinomas); in all other white women the ratio is 1:1.29, and in negro women it is 1:5.2 (National Cancer Institute, Washington, 1952). In Japan the ratio is 1:24.4 (KAISER, 1969). Endometrial carcinoma predominately develops after the menopause (80 per cent). As calculated from about 12,000 cases, which were compiled from the literature (DALLENBACH-HELLWEG, 1964) and supplemented by additional cases, the average age of the patients is 57.5 years. Only about 2 per cent of all carcinomas of the corpus uteri are found in women under 40 years (SOMMERS *et al.*, 1949; DOCKERTY *et al.*, 1951; HUSSLEIN and SCHÜLLER, 1952; KEMPSON and POKORNY, 1968). It has been described in girls under 12 years but is extremely rare (MARTINS, 1960).

A large percentage of the women who develop endometrial carcinoma have **endocrine disturbances;** it is particularly striking how many of them also have hypertension, diabetes mellitus, obesity, and are sterile (see Table 14). Even though the findings reported by the various investigators may not be quite comparable with one another, the large numbers of patients involved nevertheless allow us to obtain a fairly accurate survey of the subject. The menopause is often delayed (CROSSEN and HOBBS, 1935; RANDALL, 1945; GUSBERG, 1947; TAYLOR and BECKER, 1947; Speert, 1948; PALMER *et al.*, 1949; COSBIE *et al.*, 1954; WAY, 1954; PEEL, 1956; KOTTMEIER, 1959; DIEBELT *et al.*, 1962, and others). The climacterium is free of disturbing signs and symptoms of hormonal insufficiency.

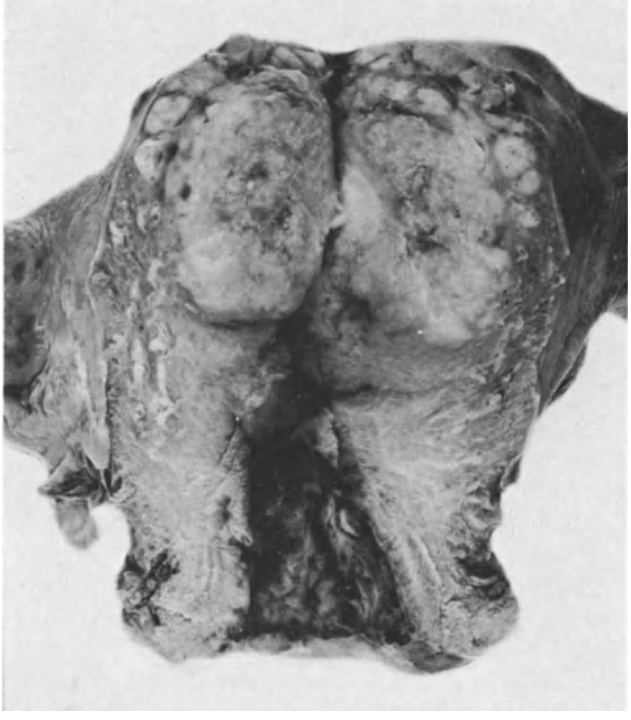


Fig. 82. A complete uterus opened to show an adenocarcinoma of the corpus endometrium that extends through the uterine wall to the serosa

Usually when examined **grossly,** carcinoma of the corpus uteri is found in the fundus, arising from the mucosa of a tubal recess. Carcinomas originating in the region of the isthmus or just above it are uncommon; according to TAYLOR and BECKER (1947) they represent 24 per cent of the corpus carcinomas. The reason for the low incidence here is probably the insensitivity of the isthmic mucosa to hormones. The tumors may project as spongy, polypoid or papillary masses into the uterine cavity. They may, however, be flat or ulcerated, or grow primarily into the uterine wall (R. MEYER, 1930). With such invasion the uterus is not always enlarged (Fig. 82). Growth takes place relatively slowly, and metastases often appear late.

Various authors have suggested schemas for *classifying endometrial carcinoma by stages.* We use a modified version of the widely used JAVERT and HOFAMMANN (1952) classification (see HELD, 1969) which is also identical with the F.I.G.O. (International Federation of Gynecology and Obstetrics) classification:

Stage 0: limited to the endometrium;
Stage 1: invasion of the myometrium;
Stage 2: extension into any part of the cervix;
Stage 3: extension into the fallopian tube, ovary or vagina; lymphogenous metastases, but limited to the small pelvis.
Stage 4: spread to the urinary bladder or rectum, and/or hematogenous metastases.

From the autopsies of 80 patients who had been treated for endometrial carcinoma, FISCHER (1957) found **metastases** in 80 per cent. Structures and organs most frequently involved were: lymph nodes (47.5 per cent), parametrium (30.5 per cent), peritoneum (31.2 per cent), liver (21.2 per cent), pelvic connective tissue (18.7 per cent), urinary bladder (16.2 per cent), and rectum (13.7 per cent). In 12.5 per cent the vagina, bowel and pleura were invaded, the lungs in 10 per cent. In only 2.5 per cent of the cases were metastases disclosed in the ovaries, stomach and pancreas. Involvement of the kidney or brain was even less. Other investigators reported a higher incidence of ovarian metastases (JAVERT and HOFAMMANN, 1952: 11.8 per cent; RYDEN, 1952: 8.4 per cent; BERGSJÖ, 1962: 9 per cent; DAVIS, 1964: 7 per cent). According to HARNETT (1949), as well as to RANDALL and GODDARD (1956), distant metastases (Stage 4) develop in only 9.4 per cent of all patients with endometrial carcinoma. PIVER (1966) found, however, that 26.5 per cent of patients with adenoacanthoma had metastases. The lungs (in 4 per cent of DIETZ's cases, 1958) and liver were involved most often. Other authors emphasized the frequency of involvement of lymphatics and blood vessels (JAKOBOVITS, 1956; BARBER *et al.,* 1962) or the isolated metastases to the central nervous system (LIPIN and DAVISON, 1947). Metastases to bones are rare (VANECKO *et al.,* 1967). In HARNETT's (1949) series, the endometrial carcinoma remained localized to the body of the uterus in 65.6 per cent of the patients. Compared with carcinomas of other regions, endometrial carcinomas metastazise infrequently but are more often associated with a second primary tumor, e.g., of the ovary, breast, or rectum. These may or may not resemble the endometrial tumor histologically. If they do, one should never forget that possibility to avoid misdiagnosing a second primary as a metastasis (JAHODA and TATRA, 1972).

Microscopically, endometrial carcinoma may be divided into three main types: the mature well-differentiated adenocarcinoma, the immature poorly differentiated adenocarcinoma, and the adenoacanthoma. The two minor types, both quite rare, are the clear-celled adenocarcinoma and the mucoepidermoid adenocarcinoma. Eighty-six per cent of all endometrial carcinomas are of the mature and immature types (HERTIG and GORE, 1960). Depending on the thoroughness of the histological examination, the adenoacanthoma may constitute from 6.8 per cent (MARCUS, 1961) to 43.7 per cent (TWEEDDALE *et al.,* 1964; DOBBIE *et al.,* 1965: 5.5 per cent; BOUTSELIS *et al.,* 1963: 7 per cent; HERTIG and GORE, 1960: 14 per cent; DAVIS, 1964: 14 per cent; JAVERT and RENNING, 1963: 16 per cent; CHARLES, 1965: 37.1 per cent; see the last for further references). NG *et al.* (1973) reported that over a 30 year period the adenoacanthomas had increased from 12.6% to 32.8%. ROBBOY and BRADLEY (1979) suggested that increase might be related to the growing use of estrogen therapy.

In deciding type of therapy and in evaluating prognosis, not only is the staging of the tumor important, but also its histological grading, as recent studies have shown. We distinguish:

Grade I: mature or well-differentiated adenocarcinoma.
Grade II: mature adenocarcinoma with regions of solid carcinoma.
Grade III: immature or poorly differentiated adenocarcinoma
clear-celled adenocarcinoma
mucoepidermoid adenocarcinoma

Although the types of glands and epithelial cells composing endometrial carcinomas vary considerably from tumor to tumor, it usually is easy to recognize and differentiate these carcinomas from adenocarcinomas of the cervix, which have their own characteristic histological patterns (DALLENBACH-HELLWEG and BRÄHLER, 1960). The glands of the *mature adenocarcinoma* of the endometrium usually appear slender, contain little mucus, and are lined by a pseudostratified or stratified epithelium that may grow into the lumen in a papillary fashion. Shedding of cells into the lumen ("cell secretion") frequently occurs (see Fig. 83b). The nuclei are large, at times pleomorphic, and often contain several prominent nucleoli. Mitoses are numerous. The cytoplasm is sparse. In their fine structure, however, these cells do not differ strikingly from those of the normal endometrium (THRASHER and RICHART, 1972; AYCOCK *et al.,* 1979). In cytologic smears they are, therefore, usually recognized only with difficulty. A periglandular basal lamina is always developed. According to FERENCZY (1976), even poorly differentiated carcinoma cells may be suspected to be of endometrial origin from their abundant juxtanuclear microfilaments. Usually the stroma between the tubular glands is barely visible, being reduced to slips of scanty fibers of collagen and thin capillaries (Fig. 83a). Mucin-secreting adenocarcinomas of the corpus endometrium are rare. Histologically they can be distinguished from the primary carcinomas of the endocervix by the composition of their mucopolysaccharides (TILTMAN, 1980).

In contrast, the *immature adenocarcinoma* is composed of solid sheets of cells in which one may often find primitive glands by using the PAS stain. These glands appear as pseudorosettes, containing in their centers small amounts of mucus about which the elongated tumor cells radiate (Fig. 84). All forms

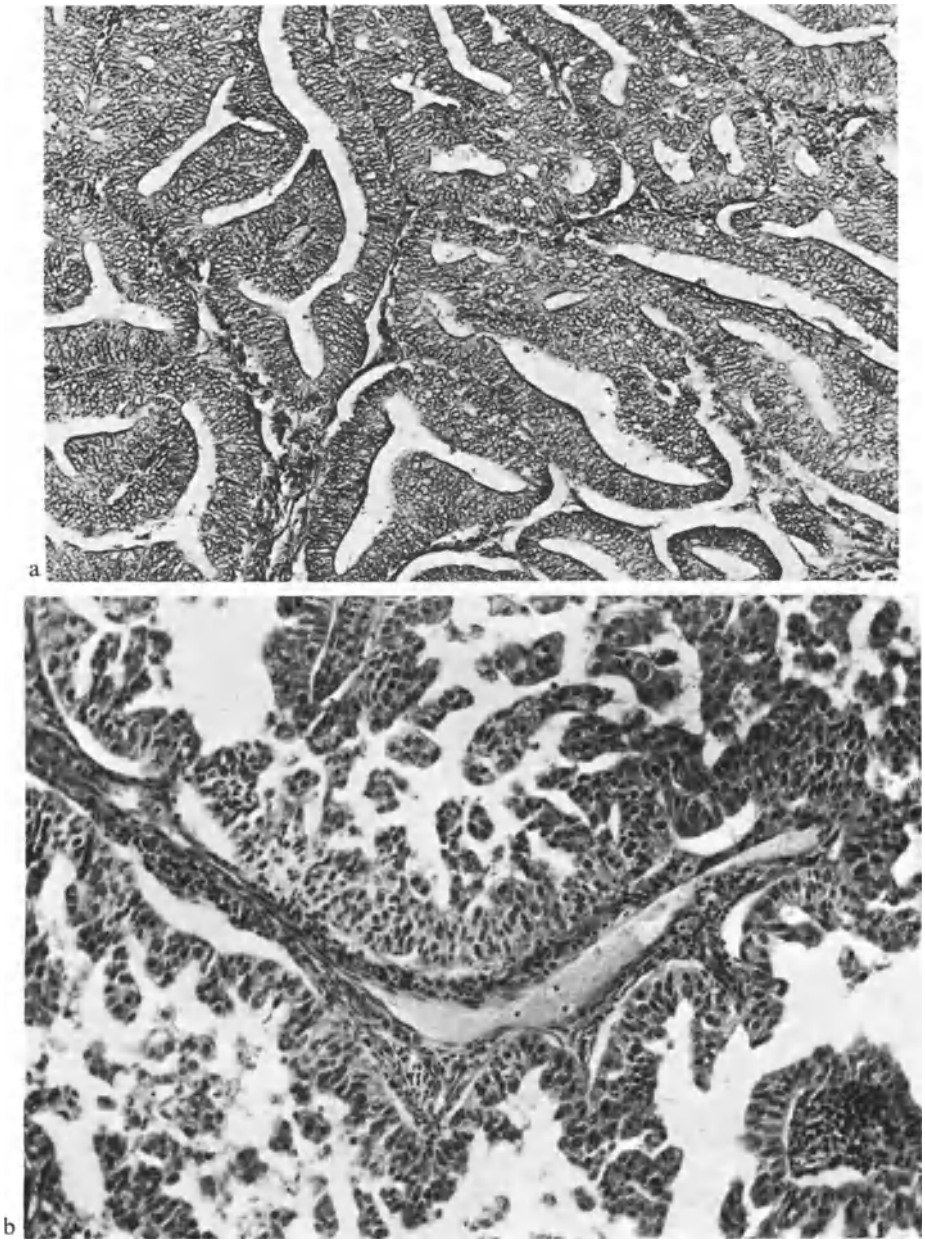


Fig. 83a and b. A mature adenocarcinoma of the endometrium. (a) Coarsely papillary. (b) Finely papillary, with intraluminal papillae

of glands may be present, however, from that most primitive type to small alveolar structures, to large well-developed acini. An adenocarcinoma often consists of immature and mature components, whose striking differences are best contrasted when the two border one another (Fig. 85).

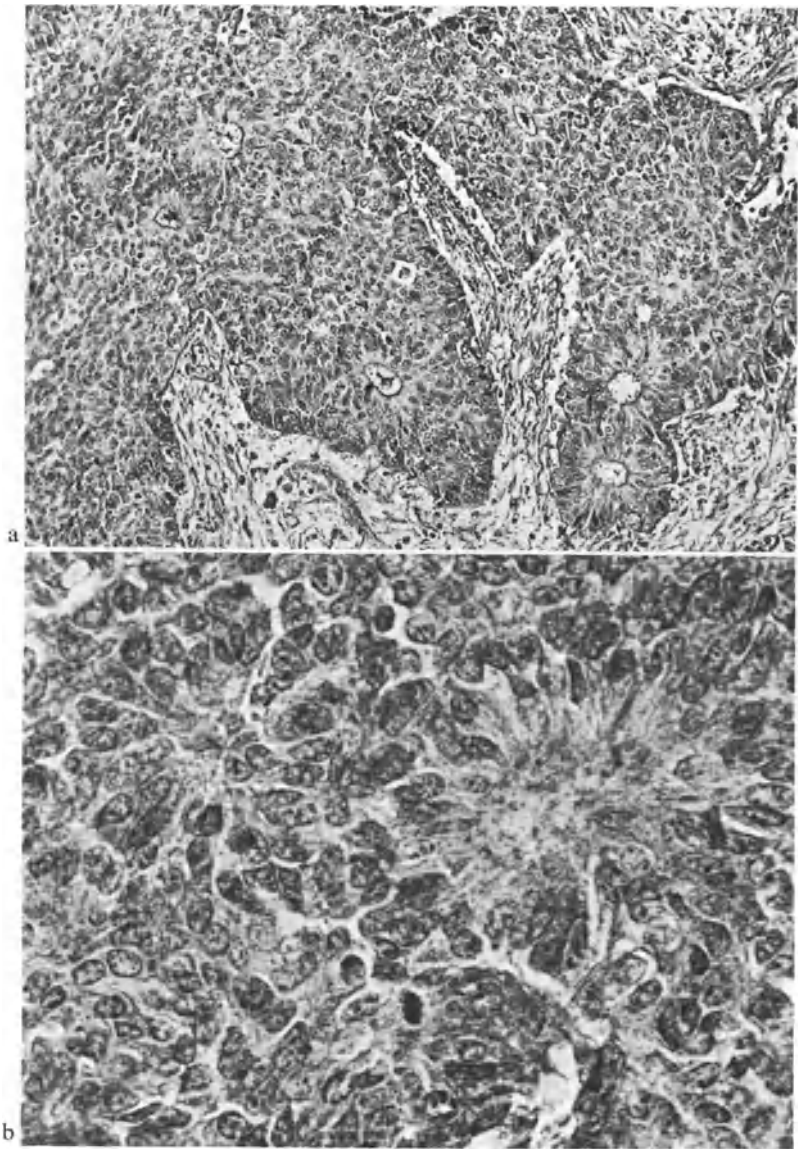


Fig. 84 a and b. Immature adenocarcinoma of the endometrium, composed of solid cords of cells with some nuclei arranged in pseudorosettes and a suggestion of primitive gland formation. (a) Low magnification. (b) Higher magnification

Primary adenocarcinomas of the endometrium composed of *clear cells* are relatively rare and usually develop in the senile patient beyond the seventh decade of life. According to their degree of differentiation, the clear cells may form solid sheets, or glands, or papillae. The solid forms resemble the clear-celled carcinomas of the cervix and like these are incorrectly referred to as mesonephroid adenocarcinomas (Janovski and Weir, 1962; Villa Santa, 1964; Dobbie *et al.*,

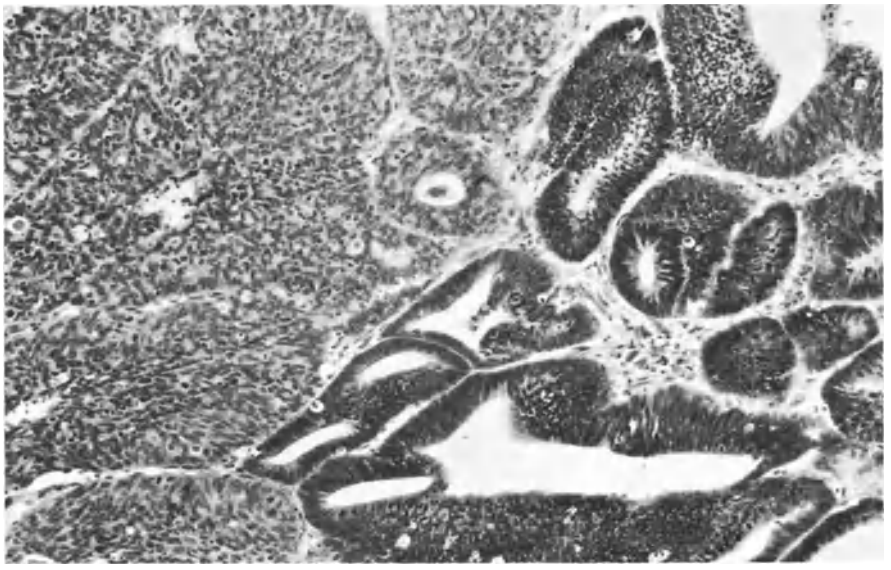


Fig. 85. Adenocarcinoma of the endometrium composed of mature and immature parts that are readily distinguished

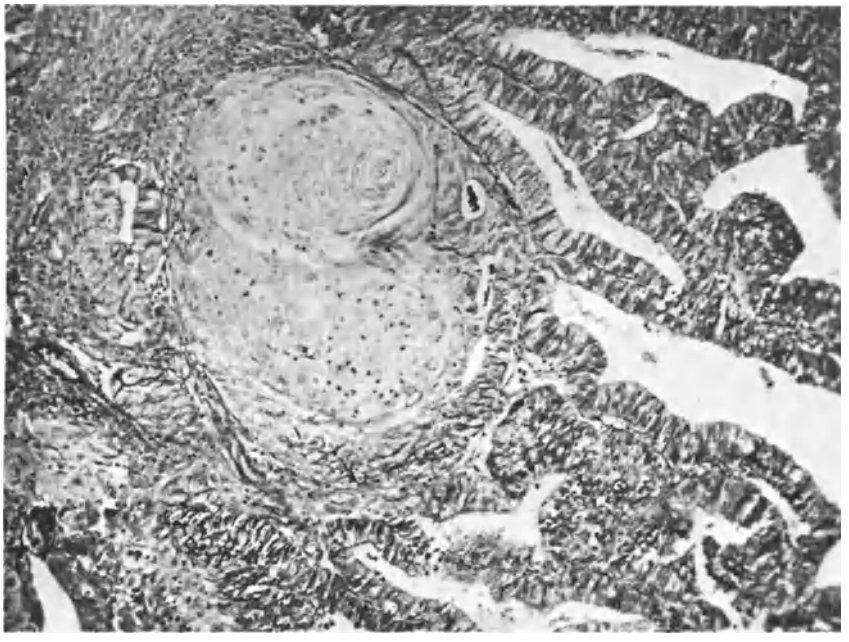


Fig. 86. Adenoacanthoma of the endometrium with nests of squamous cells among the glands

1965; RUTLEDGE *et al.*, 1965). Two possibilities exist for the origin of these clear cells: either they may originate from endometrial epithelial cells that secrete excessive amounts of glycogen (see cases of KAY, 1957) owing to abnormal differ-

entiation but unrelated to progesterone stimulation, or they may be tumor cells stemming from the Müllerian epithelium and still possessing multiple potentialities (see Table 15). In favor of a Müllerian origin is their ultrastructural similarity to the clear cell carcinomas of the ovary, cervix and vagina (SILVERBERG and DEGIORGI, 1973; RORAT *et al.*, 1974; ROTH, 1974; KURMAN and SCULLY, 1976; HORIE *et al.*, 1977). On the other hand, their structural identity is incomplete (EASTWOOD, 1978), perhaps owing to effects exerted by the respective tissue of origin. Occasionally some of their cells resemble those of an Arias-Stella-reaction, presumably because of a hyperstimulation from postmenopausal secretion of gonadotropin (see Fig. 88).

The term *adenoacanthoma* (Adenocancroid; HERXHEIMER, 1907) should be reserved for that very characteristic type of adenocarcinoma composed of endometrial-type glands and nodules or islets of mature squamous epithelium. The tumor must be distinguished from the mixed types of cervical carcinomas made up of both glandular elements and squamous epithelium in various stages of differentiation (see p. 214). Histologically the adenoacanthomas are often found to be papillary (Fig. 86). The epithelium forming the glands, most of which are well-differentiated, is pseudostratified or stratified and frequently grows as papillae. The glandular lumina are usually narrow and contain either scanty mucus or none at all. The nodules of squamous epithelium mingle with the cells of the glands from which they apparently arise; some nodules contain parakeratotic horn-pearls, others often reveal intercellular bridges. Opinions vary greatly about the origin of these nodules of squamous epithelium. Observations on their development and their morphological behavior suggest that they arise by metaplasia from the columnar epithelium (NOVAK, 1929; TWEEDDALE *et al.*, 1964; CHARLES, 1965; WILLIAMS, 1965). Because the histological structure of the nodules is so regular, most investigators assume they represent benign metaplasia within an adenocarcinoma. Ultrastructurally, however, they show criteria of malignant cells, with chromatin clumping of the nucleus and poorly formed tonofibrils in the cytoplasm (ALKAWA and NG, 1973). That they are potentially malignant is proved by the observation that some metastases of the adenoacanthoma not only consist of glands but often of squamous epithelium as well (CHARLES, 1965). The scanty stroma present in the adenoacanthoma often contains abundant foam cells (DALLENBACH-HELLWEG, 1964; TWEEDDALE *et al.*, 1964; CHARLES, 1965; see p. 175). In rare instances, the nodules of squamous epithelium may be the predominant component of the tumor, which then resembles a *mucoepidermoid adenocarcinoma*; it may, therefore, be diagnosed as such originating in the endometrium (Fig. 87). It is the same as the adenosquamous carcinoma of the Anglo-American literature. In recent years reports suggest this tumor is steadily increasing (SALAZAR *et al.*, 1977). It is highly malignant, allowing a five-year survival rate of less than 20%. BLAUSTEIN *et al.* (1978) described the mucoepidermoid type of endometrial carcinomas in five of ten patients, all who had as well primary intraductal breast carcinomas.

It is extremely rare to find a *squamous-cell carcinoma* of the endometrium in a uterus in which the cervix and portio vaginalis are normal. KERGER (1949) suggested that such tumors arose from islets of squamous epithelium left behind as embryonic remnants of the Müllerian epithelium (for additional references

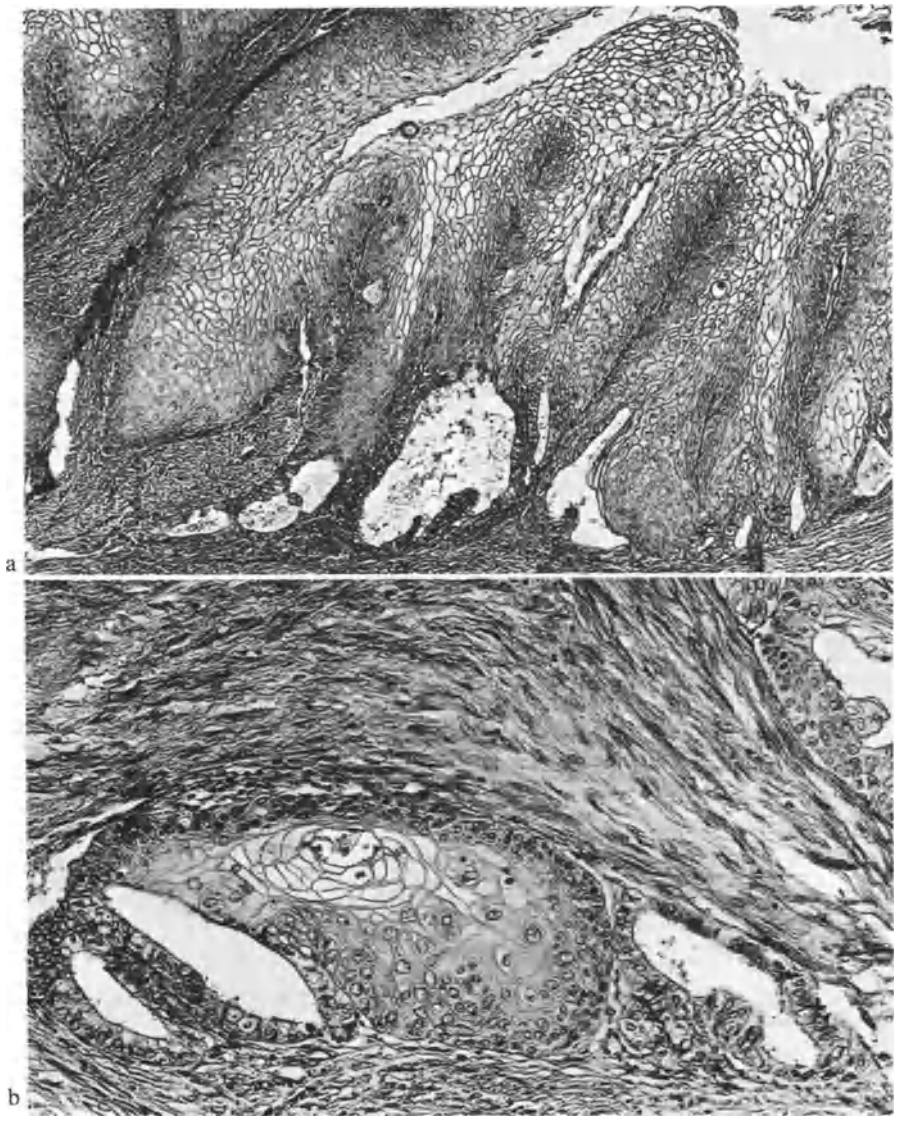


Fig. 87a and b. Mucoepidermoid carcinoma. (a) low magnification: at the surface it resembles an "Ichthyosis uteri". (b) High magnification: adenocarcinomatous cells differentiating into epidermoid carcinoma (socalled squamous metaplasia)

refer to CORSCADEN, 1956; CHU *et al.*, 1958; PERIS *et al.*, 1958; BARNETT, 1965; KAY, 1974; MELIN *et al.*, 1979). It is also possible these tumors develop from an ichthyosis uteri (RUGE, 1918; HOPKIN *et al.*, 1970; SELTZER *et al.*, 1977), the result of a generalized metaplasia of the glandular epithelium. A primary squamous cell carcinoma of the endometrium has never been reported in a woman before the menopause (WHITE *et al.*, 1973).

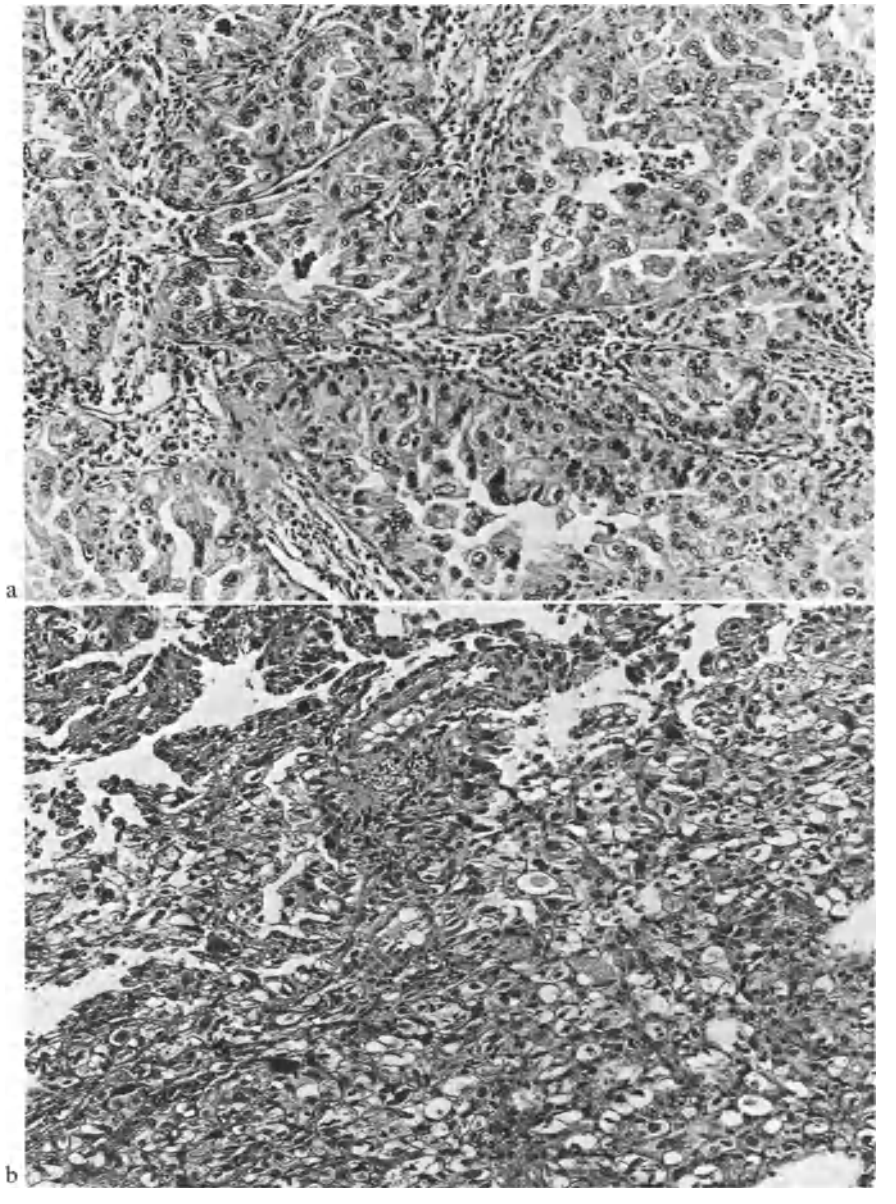


Fig. 88a–d. Adenocarcinoma of the senile woman. (a) Clear-cell type with nuclear changes like those of an Arias-Stella-Phenomenon. Patient 77 years old. (b) Poorly differentiated clear-cell carcinoma producing glandular structures. Patient 76 years old. (c) Papillary adenocarcinoma with villus-like structures. Grossly it also resembles placental tissue. Patient 72 years old. (d) Oxyphilic ("oncocytic") appearance of glandular epithelial cells of a papillary adenocarcinoma. Patient 74 years old

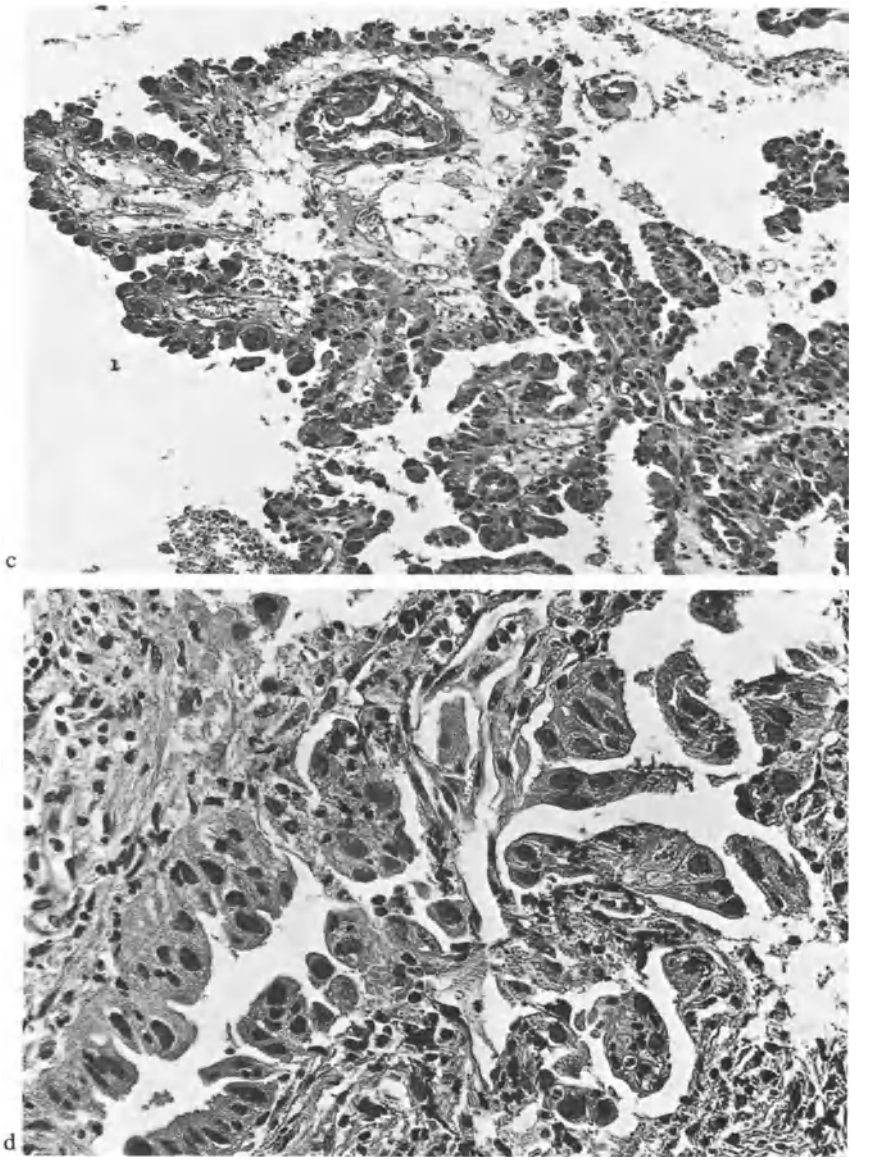


Fig. 88c and d. Legend see opposite page

Although the endometrial carcinoma of the early postmenopausal patient often resembles the normal endometrium, the endometrial carcinoma of the *senile patient* bears little resemblance to it. Grossly, such a tumor often looks like placental tissue and histologically consists of bushy, branched papillae clothed with several layers of small polygonal epithelial cells (Fig. 88c). In other types cellular pleomorphism may be prominent (Fig. 88a+d). Regions of clear cells are frequently seen (Fig. 88b). In Liu's (1972) series, the average age

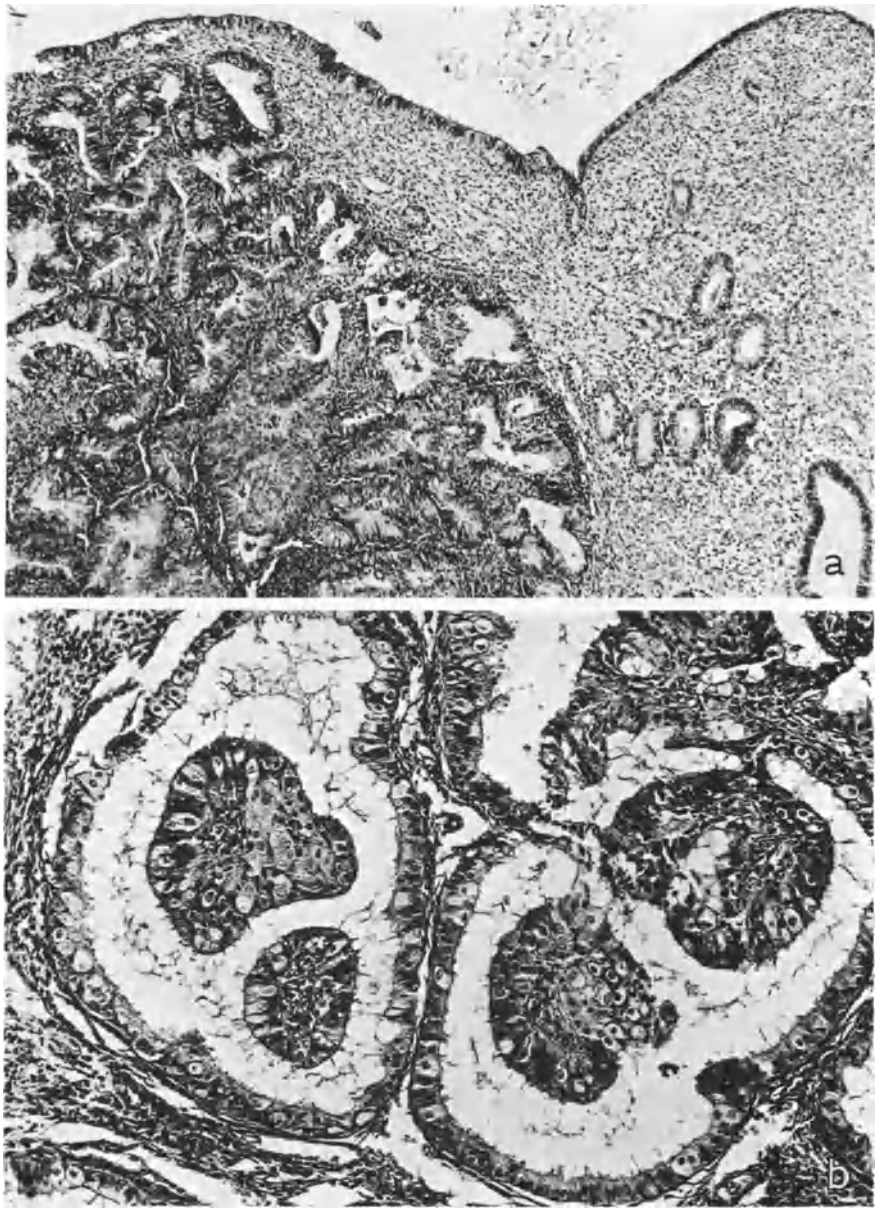


Fig. 89a and b. Circumscribed carcinoma-like adenomatous hyperplasia in a 32 year old patient, (a) replacing the stroma, (b) the hyperplastic epithelium forming distinct papillae in glandular lumina

of patients with the anaplastic embryonal carcinomas of the endometrium was 73 years.

The **histological diagnosis** of a mature well-differentiated adenocarcinoma in **women under forty years of age** must be made with great caution. Such rare

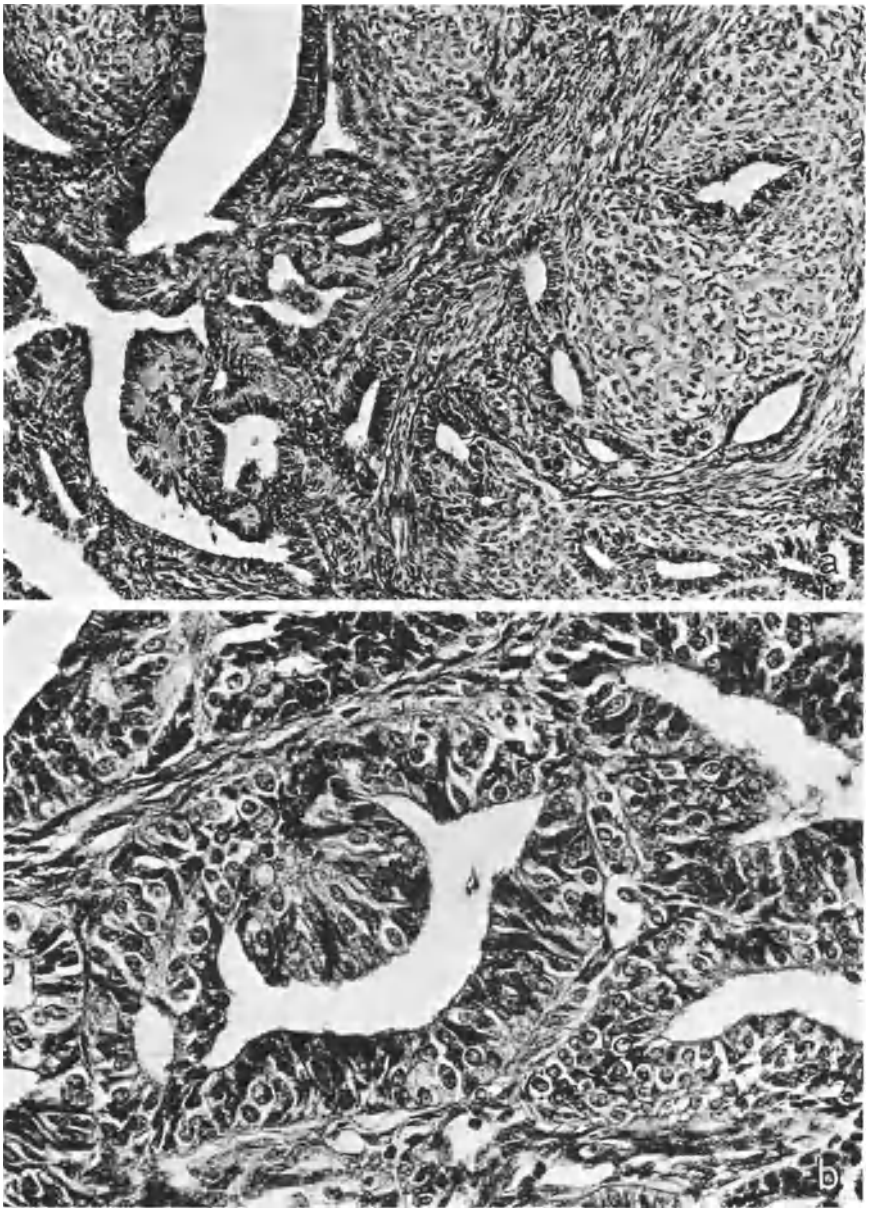


Fig. 90a and b. Carcinoma-like adenomatous hyperplasia, a borderline case, developing in a 37 year old patient after 17 years of estrogen therapy. (a) The glands disarranged, (b) some showing papillary overgrowth into their lumina

endometrial carcinomas in patients of that age-group may be diagnosed with certainty, with all therapeutic consequences implied, only if immature components predominate; that is, when poorly differentiated regions indicate without doubt that the tumor is malignant. Clinical experience has taught us that growths,

which histologically would be classified after the menopause as unequivocal adenocarcinomas, in young women are able to regress and therefore should be regarded as adenomatous hyperplasias (ULM, 1965; GRATTAROLA, 1969, 1973; DALLENBACH-HELLWEG *et al.,* 1971; FECHNER and KAUFMAN, 1974; MOUKHTAR *et al.,* 1977). It is in such cases that our ability to judge the biology of a tumor by its histology fails us; what is decisive is the patient's age. Typical for this young age-group is the focal character of the adenomatous hyperplasia at multiple, segregated sites, which may be surrounded by almost normal endometrium (Fig. 89). Often foci of squamous metaplasia or intraluminal papillary growth develop within the atypical glandular epithelium (Fig. 90). The limited and focal character of this adenomatous hyperplasia may explain why it on occasions can coexist with a normal pregnancy (KARLEN *et al.,* 1972).

Histochemical results. The *content of* **nuclear** *DNA* in the carcinoma cells is unrelated to the grade of their differentiation (ATKIN *et al.,* 1959), but generally it is increased (FETTIG and OEHLERT, 1964; FASSKE *et al.,* 1965; FETTIG, 1965). Studies of the *chromosomes* of the carcinoma cells have revealed that some of the cells are hyperdiploid, some hypodiploid to hypotetraploid (WAKONIG-VAARTAJA and HUGHES, 1967); anomalous numbers are increased as compared with non-malignant endometria (BAKER, 1968). In contrast, STANLEY and KIRKLAND reported endometrial carcinomas to be chiefly diploid or pseudodiploid, a result quite different from that for carcinomas of other organs. TSENG and JONES (1969) also found diploid or pseudodiploid sets of chromosomes in endometrial carcinomas that were like those sets found in glandular-cystic hyperplasia and adenomatous hyperplasia. From their results they concluded that endometrial carcinoma was biologically unique.

The **cytoplasm of the carcinomatous glandular epithelium** may be either clear or dark, and may contain *glycogen* (ELTON, 1942; ATKINSON *et al.,* 1952; MCKAY *et al.,* 1956), glycoproteins, or mucus (DALLENBACH-HELLWEG and BRÄHLER, 1960; SALM, 1972) (see Table 10). Often the amount of mucus or glycogen parallels the degree of cellular differentiation (CRAMER and KLÖSS, 1955; LEWIN, 1961; STRAUSS, 1963) and may vary greatly within a tumor or even within one carcinomatous gland.

In 80 per cent of the mature adenocarcinomas, as in the normal endometrium, the *acid mucopolysaccharides* are localized at the apical end of the glandular cells. Thus by staining for mucus it is possible to distinguish a mature endometrial carcinoma from an endocervical carcinoma, since the mucus in the cervical carcinoma is distributed in the majority of cases throughout the cytoplasm of the carcinomatous cells (SORVARI, 1969). In addition, the acid mucopolysaccharides of the endometrial glands differ histochemically in quantity and quality from those of the glands of the cervix (MOORE *et al.*, 1959). The most common type of mucins in endometrial carcinoma are sulphomucins. Through loss of acidic groups the mucus in glandular lumina of the corpus carcinoma often is non-metachromatic, contrasting thus with the extracellular mucus in the non-carcinomatous endometrium. The cytoplasmic RNA in the cells of the endometrial carcinoma is increased (ATKINSON *et al.*, 1949; ATKINSON, 1955; MOOKERJEA, 1961; FRAMPTON, 1963), but varies from one part of the tumor to another (GROSS, 1964) as electronmicroscopic studies have confirmed (NILSSON, 1962). The number

Table 10. Histochemical results in benign and malignant conditions of the endometrium

	RNA	Phosphatase		Ester-ase	Glyco-gen	Glyco-protein	Lipid	Foam Cells (in per cent)
		alk.	acid					
Proliferative Phase	+	++	(+)	+	(+)	(+)	(+)	–
Secretory Phase	(+)	(+)	++	+	++	+	(+)	–
Glandular-cystic Hyperplasia	++	++	(+)	(+)	(+)	++	++	30.0
Adenomatous Hyperplasia	++	++	(+)	(+)	(+)	++		53.0
Early carcinoma	(+)	(+)	++	++	(+)	(+)		40.9
Adenocarcinoma	++/(+)	+/(+)	++/(+)	++	++/(+)	++/(+)	++	38.2

and size of the *mitochondria* differ from cell to cell (FASSKE *et al.*, 1965; WESSEL, 1965), their cristae are few and irregular. Although the ends of the *Golgi complex* consist of ballooned, double lamellae, they show no secretory function. The *ergastoplasm* is poorly developed, containing an electron-dense substance. In the cytoplasm of mature carcinoma cells there are, in addition, numerous *osmiophilic granules*. The cells of immature carcinomas have unusually well-developed, basal cytoplasmic processes.

The activity of the *alkaline phosphatase* decreases as the carcinoma becomes less differentiated (ATKINSON and GUSBERG, 1948; HALL, 1950; MCKAY *et al.*, 1956; MOOKERJEA, 1961; LEVINE, 1963; KUCERA, 1964; PFLEIDERER, 1968). The activity of *17β-hydroxysteroid dehydrogenase* also decreases as the carcinoma becomes less mature (POLLOW *et al.*, 1975). The activity of the *acid phosphatase* is usually increased (MCKAY *et al.*, 1956) but occasionally may also be decreased (GOLDBERG and JONES, 1956). The *esterase* activity varies greatly (GROSS, 1964), at times being increased (MCKAY *et al.*, 1956). The same holds true for β-glucuronidase, phosphoamidase and most of the *dehydrogenases* (ISHIHARA *et al.*, 1964; MOUKHTAR and HIGGINS, 1965; TAKI *et al.*, 1966; THIERY and WILLIGHAGEN, 1967; FILIPE and DAWSON, 1968; PFLEIDERER, 1968). JIRASEK and DYKOVA (1964) reported an abnormal localization of esterase and acid phosphatase along the basement membrane of the glandular epithelium and concluded it indicated atypical metabolic processes. From the results of extensive studies, PFLEIDERER (1968) pointed out that there was no enzyme reaction characteristic of endometrial carcinomas. The results of the reactions vary greatly from one region of the tumor to another and depend as well on the age of the patient. Only in the actively growing parts of the tumor do enzymes become activated, which participate either in oxidative catabolism or in the simultaneous proteolytic digestion of degenerating connective tissue.

Lipids and *cholesterol* are present in large amounts in the **stroma** of the endometrial carcinoma (ATKINSON, 1955; LONG and DOKO, 1959), a fact most likely correlating with the appearance of lipid-containing *foam cells* in the stroma of mature adenocarcinomas (STOERK, 1906; DUBS, 1923; SCHILLER, 1927; NUNES, 1945; CHIARI, 1955). HARRIS (1958) found foam cells in 11 per cent of endometrial

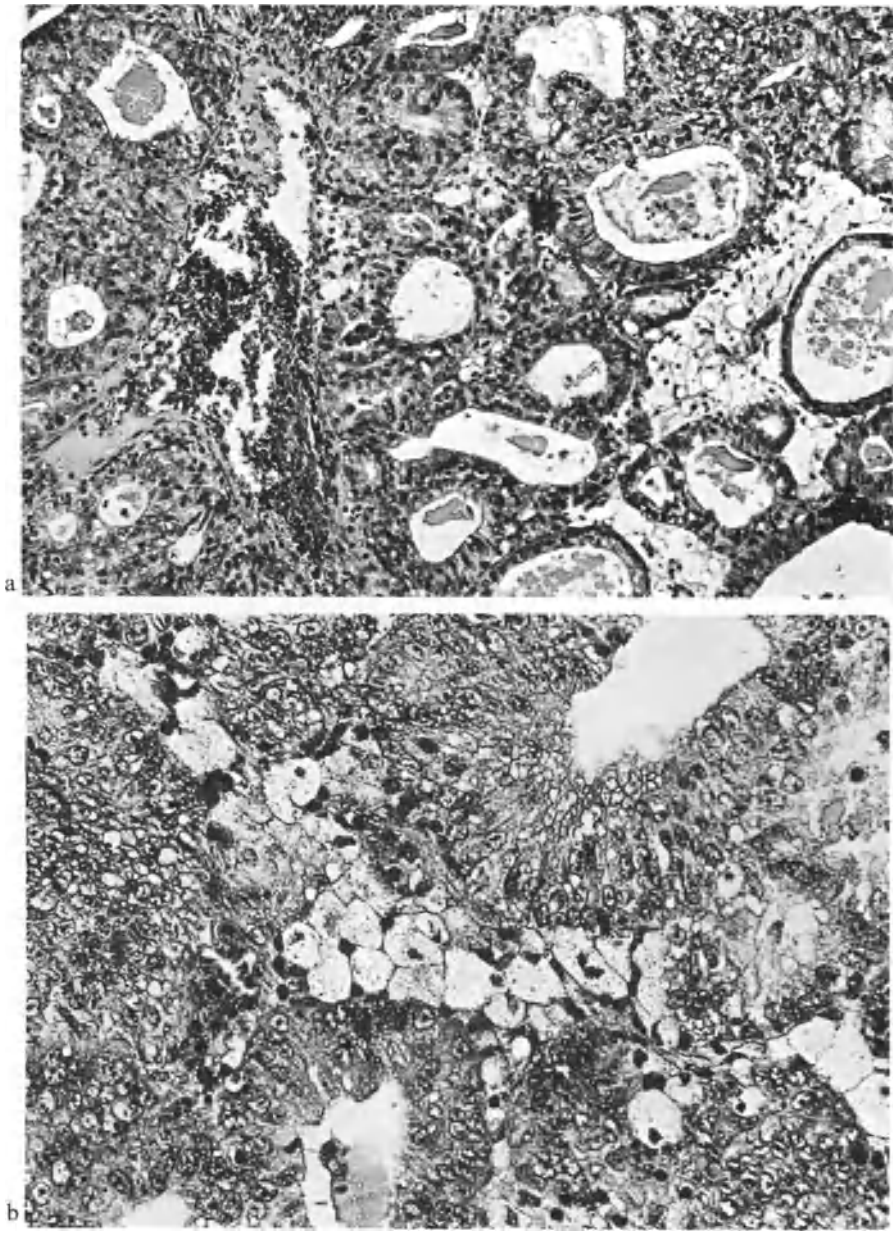


Fig. 91 a and b. Mature adenocarcinoma with foam cells in the gusset-like stretches of stroma. (a) Low magnification. (b) Higher magnification

carcinomas; KRONE and LITTIG (1959) in 13 per cent, and ISAACSON *et al.* (1964) in 43 per cent of their cases. VON NUMERS and NIEMINEN (1961) also observed foam cells in some of their cases. SALM (1962) described lipophages (most probably foam cells) in the stroma of 7.5 per cent of endometrial carcinomas but could

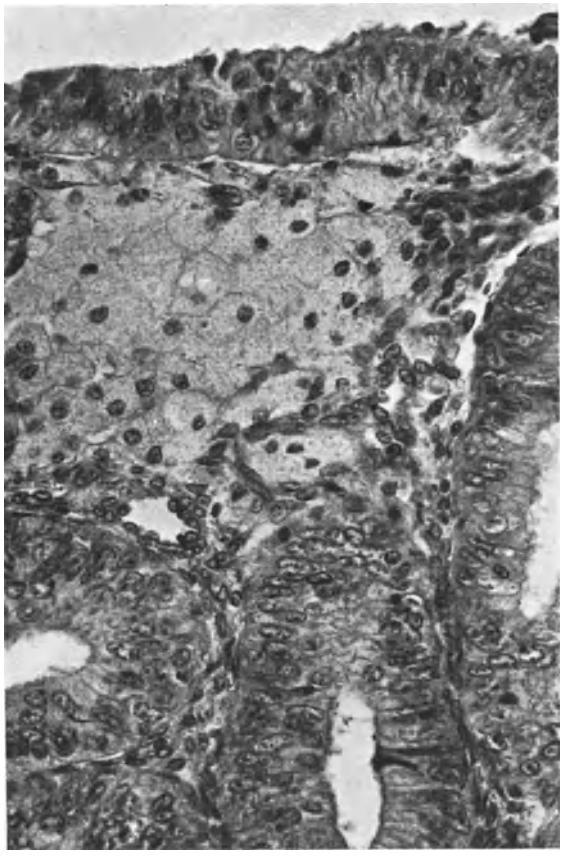


Fig. 91c. Foam cells below the surface epithelium of an adenocarcinoma

detect none in normal endometrium. He proposed that when the cells were found they strongly suggested the presence of carcinoma. We detected typical foam cells in 25 per cent of immature adenocarcinomas, in 38 per cent of mature adenocarcinomas and in 43 per cent of adenoacanthomas (DALLENBACH-HELLWEG, 1964; see Fig. 91, 92). Morphologically and histochemically they are identical with the foam cells of adenomatous hyperplasia (see p. 114ff). One may encounter all transitions, from typical foam cells to hyalinized end-forms. With the progression from adenomatous hyperplasia to carcinoma not only do the number of foam cells decrease, but also the DNA content of the stromal cells (FETTIG, 1965).

When *psammoma bodies* are found in an endometrial carcinoma, they may indicate that the tumor is a metastatic carcinoma, usually from the ovary (see p. 211). Primary *psammocarcinomas* of the endometrium (HAMEED and MORGAN, 1972) or adenocarcinomas with psammoma bodies (FACTOR, 1974; LIVOLSI, 1977) likewise may occur, but are rare, and a small primary tumor in the ovary can never be excluded with certainty. According to HITSCHMANN (1903), psammomatous bodies can develop from degenerated and calcified cells of an

epidermoid carcinoma or from micropapillary adenocarcinomas with shedding of epithelial cells, which may resemble ovarian carcinoma (see Fig. 81 b).

Apart from the extent of spread of an endometrial carcinoma at the time therapy is started, its **prognosis** in general is determined by the maturity (histological grading) of its cells. The five year survival rates of mature adenocarcinomas varied from 72–86 per cent; for immature adenocarcinomas with uniform nuclei from 45–79 per cent, and for the immature carcinomas with pleomorphic nuclei they fell to 28–58 per cent (PÜSCHEL and MÖBIUS, 1967; LIU, 1972). Within the group of well-differentiated tumors, patients with mucus-secreting endometrial carcinomas proved to have a more favorable prognosis than those with non-mucinous tumors of like structure (LEVINE, 1969); the clear-celled carcinomas showed even a worse prognosis (PHOTOPULOS *et al.*, 1979). In STOLL'S series (1957) the cure-rate for all cases was 61 per cent; in the series of CLIMIE and RACHMANINOFF (1965) and NG and REAGAN (1970) it was 63 and 69.7 per cent respectively. From the statistics of other investigators the prognosis of adenoacanthoma, owing to its earlier and more extensive metastases, was found to be less favorable than that of the adenocarcinomas (CHARLES, 1965; and others). Some authors however reported no differences (HAINES and TAYLOR, 1962; TWEEDDALE *et al.*, 1964; WILLIAMS, 1965; BADIB *et al.*, 1970). As to the prognosis of mucoepidermoid carcinomas, according to NG *et al.* (1973), only 19.2% of the women with these tumors survived five years compared with 72% who had well-differentiated adenocarcinomas. Independent of the histological type, a five-year cure was observed in 80–98 per cent of the women with a tumor at Stage 0. The cure-rate for tumors at Stage 1 was 66–78 per cent, at Stage 2 from 6–56 per cent; at Stage 3 and 4 no patients survived five years (BAILAR, 1961; THIEDE and LUND, 1962; JAVERT and RENNING, 1963; DOBBIE *et al.*, 1965; FRANZ, 1965). In addition to the histologic differentiation and to the stage of the tumor, the patient's age and the therapeutic management influence the prognosis. As reported in a clinical study of 355 endometrial carcinomas, the five year survival rate following hysterectomy and bilateral salpingo-oophorectomy proved more favorable: 83 per cent for tumors at Stage 1, 79 per cent at Stage 2, 42 per cent at Stage 3 and 13 per cent at Stage 4 (MILTON and METTERS, 1972). As compared with radical surgery, the prognosis after radiation therapy is much less favorable (SALL *et al.*, 1970; and others). Adjuvant radiation therapy with hysterectomy provides no better prognosis than hysterectomy alone (FRICK *et al.*, 1973). To review all reports of therapy-studies for stages 1–4 published in recent years, would far exceed the scope set for this monograph. The pathologist should realize, however, that besides a precise histological classification of the tumor, the clinician needs to know how far it has invaded the myometrium, in order to select the best therapy for that patient under study (SÖDERLIN, 1975; SALAZAR *et al.*, 1978). The particularly favorable prognosis of endometrial carcinoma in women under 40 years of age may be related in part to the mistake in diagnosing adenomatous hyperplasia as cancer (see p. 174). Regardless of the stage of growth or the type of treatment, endometrial carcinoma recurs in about 14 per cent of all cases (DEDE *et al.*, 1968).

Precursors of endometrial carcinoma. Like carcinomas in other parts of the body, most endometrial carcinomas are preceded by a precancerous state. To

Table 11. Evaluation of significance of endometrial carcinoma precursors (cf. p. 193)

I. Precancerous lesions in the endometrium:
a) facultative:
irregular proliferation
circumscribed and diffuse glandular-cystic hyperplasias
b) relative obligatory:
adenomatous polyps
circumscribed adenomatous hyperplasias
juvenile adenomatous hyperplasias
diffuse adenomatous hyperplasias
true stromal hyperplasia (rare)
II. Early carcinoma of the endometrium

determine which lesions may occur as precursors, three approaches are available for investigation (HERTIG *et al.*, 1949):

1. A retrospective approach by studying from previous curettages the development of the carcinoma.

2. A prospective follow-up of the patient after the first curettage revealed one of the types of hyperplasia.

3. A coincidental (concurrent) study of changes in those regions of the endometrium not involved by the corpus carcinoma.

The compilation and review of such studies reported in the world literature revealed interesting results (DALLENBACH-HELLWEG, 1964; SHERMAN and BROWN, 1979). The *retrospective method of study* proved to be the most informative. Most authors found that in a large percentage of their patients the endometrial carcinoma had been preceded by adenomatous hyperplasia. The percentage in whom the tumor was preceded by glandular-cystic hyperplasia, adenocarcinoma in situ, or polyps of the endometrium was somewhat smaller. In *the prospective studies* only a small number of women with glandular-cystic hyperplasia developed endometrial carcinomas; the number was significantly higher in those with adenomatous hyperplasia and highest for adenocarcinoma in situ.

The values for the prospective method of study generally are low because once the diagnosis of hyperplasia is made the practice is to treat promptly,

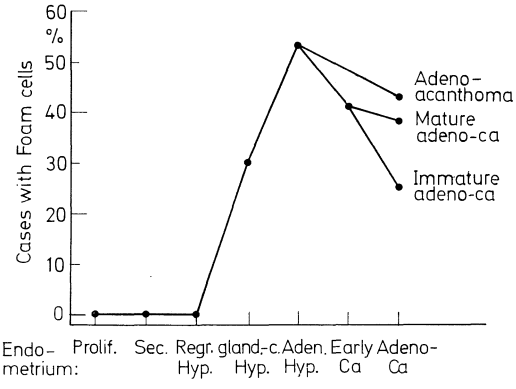


Fig. 92. Relative frequency of foam cells in hyperplasia and carcinomas of the endometrium

not to wait. *A study of the coincidental occurrence* of various forms of hyperplasia in regions of the endometrium uninvolved by the corpus carcinoma yields results comparable to those of the retrospective approach of study. Most of the changes found are those of adenomatous hyperplasia (see Fig. 93). In general the non-carcinomatous regions have a higher mitotic activity and a greater tendency to proliferate than an equivalent endometrium (KAISER and SCHNEIDER, 1968).

How are we to explain why *glandular-cystic hyperplasia* in the prospective studies terminates as carcinoma in only a low percentage of cases but in the retrospective and coincidental studies is found in a higher percentage of carcinomas? The explanation is quite simple. Most of the glandular-cystic hyperplasias occurring before the menopause are harmless. That is, glandular-cystic hyperplasia merely represents a transitory disturbance that develops during the short period of hormonal imbalance at the beginning and at the end of the reproductive years. Occasionally, however, glandular-cystic hyperplasia may persist, especially after the menopause, and under long-standing, unopposed hormonal stimulus may become an adenomatous hyperplasia, which may then undergo change to carcinoma. Consequently, we should not be surprised that in a fair percentage of corpus carcinomas (concurrent study) we would find a glandular-cystic hyperplasia in parts of the endometrium uninvolved by the tumor. Even when the adenomatous hyperplasia has already become a carcinoma, it is quite possible to detect remnants of a glandular-cystic hyperplasia of many years standing in some regions of the endometrium. Applying the same assumptions, we may explain the higher percentage of glandular-cystic hyperplasia revealed by the retrospective study. From the studies of NOVAK and YUI (1936), NOVAK (1956) believed it was important for the prognosis to distinguish clearly between glandular-cystic hyperplasia *before* the menopause and that developing *after* the menopause, which he regarded as precancerous (36 of his 815 cases). In these 36 patients he observed endocrine disturbances like those seen in the patients with endometrial carcinoma. On the other hand, hyperplasia in young women, although a rare disease, should be considered a potential precancerous lesion, because of the frequent endocrine disturbances accompanying it. In a series of young patients (between 15 and 35 years old) with hyperplasia, 14 per cent developed an adenocarcinoma 1 to 14 years after the initial diagnosis (CHAMLIAN and TAYLOR, 1970). According to HERTIG and GORE (1963), women developing glandular-cystic hyperplasia before the menopause have a ten-fold greater chance of developing a carcinoma many years later than the average women. Although not common, the development of a carcinoma from a hyperplasia certainly is not merely accidental. The studies cited above indicate that when viewed from the aspect of the carcinoma, glandular-cystic hyperplasia is indeed a precursor although in itself in the great majority of occurrences (during adolescence, climacterium) a benign process. These two ways of looking at glandular-cystic hyperplasia often are not sharply defined in the literature, leading thus to misunderstandings about the prognostic importance of that type of hyperplasia (WINTER, 1950; BEHRENS, 1954; KOFLER, 1954; RÜTTNER and LEU, 1954; SCHRÖDER, 1954; RITZMANN and HILLEMANNS, 1977).

The situation is quite different for *adenomatous hyperplasia,* which was initially described under that term by GUSBERG (1947). With all three approaches of

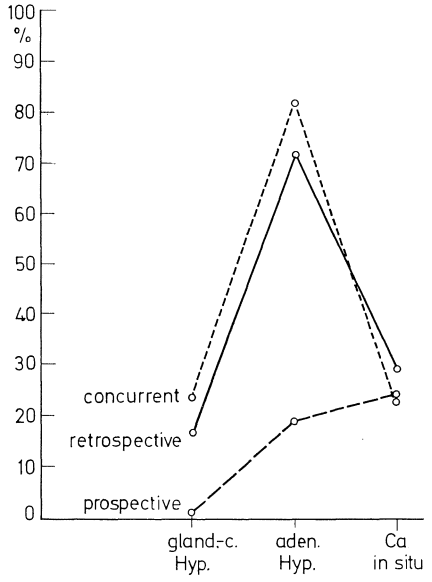


Fig. 93. The prospective, retrospective, and concurrent frequencies of hyperplasias associated with endometrial carcinoma

study (retrospective, prospective, and concurrent) the percentage of adenomatous hyperplasias is found to be very high. The possibility it is a precursor of carcinoma therefore is great. In support of that idea are the pronounced atypical proliferations of glands and glandular epithelium occasionally found in adenomatous hyperplasia that make it extremely difficult if not impossible to distinguish adenomatous hyperplasia from carcinomas (see Fig. 60). Patients with adenomatous hyperplasia present clinical manifestations, especially those of hormonal abnormalities, which are like those of early endometrial carcinoma (GUSBERG *et al.*, 1954; GARNET, 1958; GUSBERG and KAPLAN, 1963; see Table 14). As the prospective studies suggest, in a small percentage of patients adenomatous hyperplasia does regress without therapy. That implies adenomatous hyperplasia is not an irreversible precancerous condition and probably depends on a hormonal stimulus for its progression. BEHRENS (1956) observed that the adenomatous hyperplasias with atypical epithelial cells but without atypical glands transformed later into a carcinoma much less often than those with both atypical cells and atypical glands. The glands of the adenomatous hyperplasia and those of the subsequent carcinoma are similar; that is, of the same variety. Numerous reports of large series of cases and single observations have been published on the progression of adenomatous hyperplasia into carcinoma (review of literature, see DALLENBACH-HELLWEG, 1964).

Adenocarcinoma in situ (HERTIG *et al.*, 1949) is found most frequently in the prospective method of studies, evidence strongly suggesting that it is an early but irreversible neoplastic lesion. From our follow-up studies of women with such lesions (DALLENBACH-HELLWEG, 1979 cf. p. 122), and from analogies

made with comparable early neoplastic changes in other organs (for example, the stomach), we recommend these endometrial lesions be regarded as *early carcinomas,* and the term adenocarcinoma in situ be abolished. That renaming seems all the more logical and valid, since its glandular cells are aneuploid and do push out into the surrounding stroma, explaining how metastases may occur even at this early stage.

From such considerations the majority of investigators (see review by SPEERT, 1948; BEHRENS, 1958; ANDREWS, 1961; GRAY and BARNES, 1964; FOSTER and MONTGOMERY, 1965; SHERMAN and BROWN, 1979) concluded, that adenomatous hyperplasia should be looked upon as a potential precursor of endometrial carcinoma. Even R. MEYER (1923) and SCHRÖDER (1928) referred to progressive transitions from hyperplasia to carcinoma. The transformation takes place gradually and may require years or even decades.

HERTIG and SOMMERS (1949) found that glandular-cystic hyperplasia was most common from six to thirteen years before the carcinoma became evident in curettings. Adenomatous hyperplasia was most common one to five years, and adenocarcinoma in situ three to five years before the carcinoma appeared. HALL (1957) observed similar intervals and concluded from them, that the degree of atypia might serve to indicate how long the latent period would last before a carcinoma developed. BEUTLER *et al.* (1963) noted that with hyperplasia before the menopause there was an average interval of twelve years before the carcinoma manifested itself, but with hyperplasia after the menopause only six years were required before the carcinoma was diagnosed. MÜLLER and KELLER (1957) also found atypical hyperplasia from four to fourteen years before carcinoma became apparent; consequently they preferred to regard hyperplasia Stage 0 of corpus carcinoma. Some authors (GUSBERG and KAPLAN, 1963; CAMPBELL and BARTER, 1961) ignored the term adenocarcinoma in situ, classifying instead their adenomatous hyperplasias into different groups of severity; their last group is equivalent prognostically to early adenocarcinoma.

In the precancerous endometrium it is striking how one finds glands of diverse types located next to one another. At times one may even see in one gland several types of atypical epithelial cells, each sharply delineated from its neighbor (Fig. 62).

Only a few authors (JONES and BREWER, 1941) have questioned the precancerous importance of the hyperplasias, since they have observed endometrial carcinomas in patients with a secretory endometrium. Certainly such rare cases do occur, but in most instances they indicate that the carcinoma has arisen in a corpus polyp; that is, in a focal region of hyperplasia that has behaved like a diffuse hyperplasia (Fig. 94). At times the carcinoma is sharply demarcated from the normal basalis (Fig. 95; 96b). It is not uncommon to find polyps prior to or with the carcinoma (SCHEFFEY *et al.*, 1943: in 7.8 per cent; KOTTMEIER, 1947: in 20.7 per cent; HERTIG and SOMMERS, 1949: in 12 per cent; HENRIKSEN and MURRIETA, 1950: in 26 per cent; KINDLER, 1956: in 19.3 per cent; WEBER, 1961: in 14.6 per cent; BOUTSELIS *et al.*, 1963: in 11.7 per cent of all cases). An early carcinoma may still be limited to the polyp, but usually the polyp is only one of the multicentric foci of carcinogenesis (SALM, 1972).

PETERSON and NOVAK (1956) reported that 15.5 per cent of all corpus polyps after the menopause are involved by carcinoma. HUBER (1951) found the involvement in 58 per cent, KREMER and NARIK (1953) in 16.3 per cent. ISEKI (1924), STOKES (1948), HUBER (1951), SCHRÖDER (1954), and PETERSON and NOVAK (1956) were able to show that some carcinomas had arisen in polyps. HERTIG *et al.* (1949) disclosed that 14 of their 64 adenocarcinomas

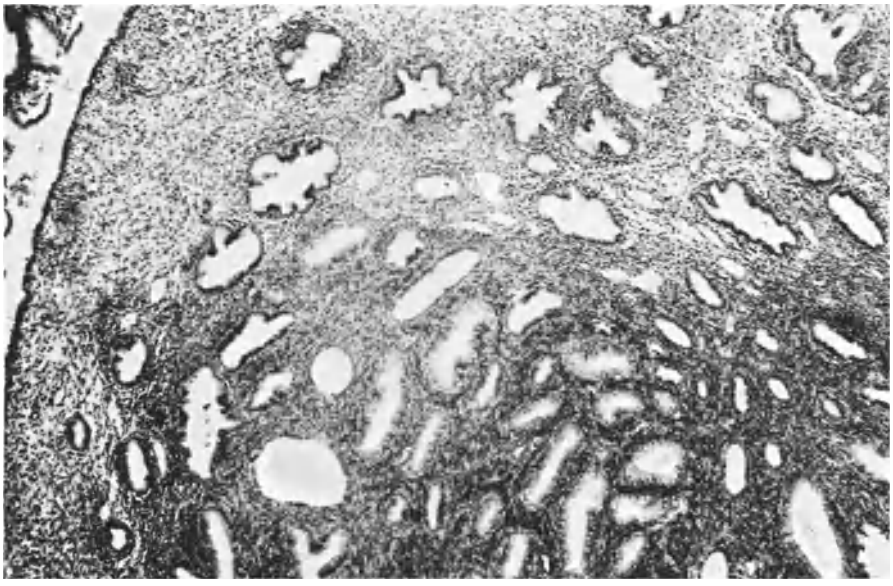


Fig. 94. Focal adenomatous hyperplasia with beginning carcinoma in the remaining secretory endometrium

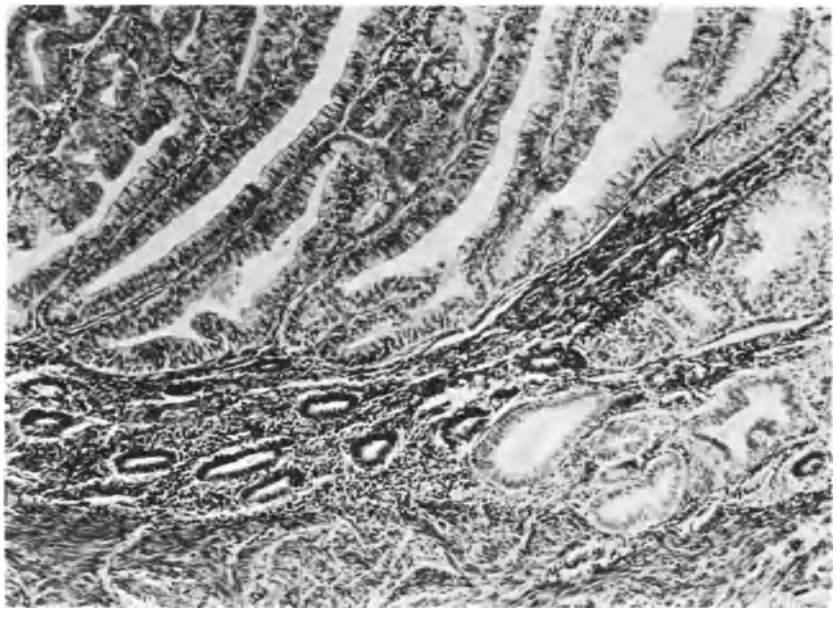


Fig. 95. Adenocarcinoma growing into the (stratum) basalis

in situ developed in a polyp. According to ARMENIA (1967), women with a corpus polyp have a nine-fold greater chance of developing a carcinoma within the next twelve years than the average woman.

HERTIG and GORE (1963; GORE and HERTIG, 1962, 1966) reported they had never seen a carcinoma develop in a normal endometrium.

Etiological concepts. If it is true that the corpus carcinoma does develop from adenomatous hyperplasia and the antecedent glandular-cystic hyperplasia, then one should expect a common etiology or at least a common disposition for these diseases. We know for a fact that hyperplasia is the response of the endometrium to hyperstimulation by excessive estrogen or to a persistent stimulation of low levels of unopposed estrogen (that is, progesterone is lacking) (SCHRÖDER, 1915; TAYLOR, 1938; LETTERER, 1948). It is not only possible to induce cystic hyperplasia in animals with estrogen (or adenomatous hyperplasia by administering it regularly over long periods; GUSBERG, 1947, 1967) but also to produce with estrogen these same changes in castrated or postmenopausal women (ZONDEK, 1940; HENRY, 1945; SCHRÖDER, 1954; BLOOMFIELD, 1957). Furthermore, the ovaries removed from women with adenomatous hyperplasia reveal in vitro an excessive production of estrogen (PLOTZ *et al.*, 1967). On the basis of comprehensive studies estrogen has been regarded for a long time as a causative factor or cofactor for endometrial carcinoma. A great many findings support such a conclusion:

Ovarian changes. The percentage of endometrial carcinomas associated with *granulosa-cell tumors or theca-cell tumors* is greater than that to be expected normally (SMITH *et al.*, 1942; SPEERT, 1948; WOLL *et al.*, 1948; NOVAK and MOHLER, 1953; KOFLER, 1954; WAY, 1954; PEEL, 1956; RANDALL and GODDARD, 1956; DAVIS, 1964; GUSBERG and KARDON, 1971). The percentage is even greater if one computes the opposite relationship—the percentage of ovarian tumors associated with endometrial carcinoma. Before the menopause that rate is 2.8 per cent (as calculated from a compilation of many large series published in the literature; for review see DALLENBACH-HELLWEG, 1964), when a corpus luteum (progesterone production) might be present to neutralize the estrogen effect. In contrast, after the menopause the rate is much higher—23.3 per cent—owing to an unopposed stimulation by estrogen. Although theca-cell tumors (thecomas) are quite rare, they are more often associated with corpus carcinomas than are the more common granulosa-cell tumors. The thecomas, moreover, may be so small they cause no palpable enlargement of the ovary, being incidentally found after total hysterectomy for endometrial carcinoma (SCHRÖDER, 1954; FATHALLA, 1967). The thecomas produce larger amounts of estrogen than the granulosa-cell tumors (BISKIND and BISKIND, 1949; INGRAM and NOVAK, 1951; JAKOBOVITS, 1963).—The reason why the percentage of endometrial carcinomas associated with feminizing ovarian tumors is not higher is explained by the fact other ovarian changes occur with endometrial carcinoma:

In 1941 SMITH reported on a *stromal hyperplasia* of the ovary, which he found in 87 per cent of his patients with endometrial carcinoma. Since then many subsequent investigators have confirmed his findings and checked them against control cases (see Table 12).

RODDICK and GREENE (1957) criticized the significance of these studies, contending that the control cases revealed less stromal hyperplasia merely because they were autopsy material. SOMMERS and MEISSNER (1957) were able to refute that criticism, however, by showing in autopsy studies that the ovaries of patients with endometrial carcinoma had

Table 12. Corpus carcinoma and stromal hyperplasia of the ovary

Author	Year	Number of patients with carcinoma	Stromal hyperplasia	
			associated with carcinoma (in per cent)	in control patients without carcinoma (in per cent)
SMITH	1941	180	87.0	
WOLL *et al.*	1948	331	84.0	44.0
MCGARVEY, GIBSON	1952	85	55.0	
NOVAK, MOHLER	1953	64	54.0	21.0
BAMFORTH	1956	81	50.0	
SCHNEIDER, BECHTAL	1956	44	52.3	35.0
HERTIG	1957	389	90.0	
SOMMERS, MEISSNER	1957	38	73.0	36.0
MARCUS	1963	100	twice as common as in the control patients	
Total number		1312	72.2	39.2

greater stromal hyperplasia than did the ovaries of control patients. NOVAK and MOHLER (1953) noted that the more mature an endometrial carcinoma appeared, the more pronounced the stromal hyperplasia of the ovaries.

WOLL *et al.* (1948) described clusters of proliferating theca cells and small socalled granulomata (HERTIG, 1944) in the hyperplastic cortical tissue. MCKAY (1962) pointed out that the stromal cells of the ovary have the potentiality to produce estrogen and can be stimulated to do so with luteinizing hormone (LH). They are most likely the precursor cells of the thecoma (MCKAY *et al.*, 1953), and in animal experiments can be stimulated to proliferate by injecting LH after estrogen levels are reduced (BISKIND and BISKIND, 1944 and 1949; KULLANDER, 1956). LEMON (1956) as well as LAJOS *et al.* (1963) proved by biochemical methods that stromal hyperplasia produced estrogen, and PROCOPÉ (1968) detected increased excretion of urinary estrogen in that condition. ZANDER *et al.* (1962) were able to demonstrate in polycystic ovaries with intense stromal hyperplasia that the formation of androgens was increased. Various investigators have been able histochemically to demonstrate steroids in the theca cells, but not in the inactive stromal cells of the ovary. MERKER and DIAZ-ENCINAS (1969) electron-microscopically found signs of steroid synthesis in the stromal cells of rats and rabbits after the animals had been stimulated with pregnant mare serum (PMS) and human chorionic gonadotropin (HCG). In his cases of diffuse thecoses, FIENBERG (1963) described transitions from stromal cells to theca cells and was able (1969) to demonstrate in all of his examples of endometrial carcinoma lipids and oxidative enzymes in the proliferating theca cells of the stroma. Likewise, MESTWERDT *et al.* (1972) reported groups of large polygonal stromal cells within the ovarian stromal hyperplasia of all endometrial carcinomas examined. The cells possessed abundant cytoplasm and showed typical ultrastructural characteristics of steroid producing cells: smooth endoplasmic reticulum, tubular-vesicular mitochondria and heterogenous lipofuscin granula, as well as enzymatic

activities characteristic of steroid biosynthesis. NOVAK *et al.* (1965) found that 66 per cent of postmenopausal women with enzymatically active stromal hyperplasia had either a hyperplastic endometrium or an endometrial carcinoma. It seems probable that stromal hyperplasia, clusters of theca cells, and thecomas are only various stages in the response to the same hormonal stimulus.

Several other investigators were impressed by the *hilar-cell hyperplasia* in ovaries from patients with endometrial carcinoma (SHAW and DASTUR, 1949; SHERMAN and WOOLF, 1959; AMES and JANOVSKI, 1963). Subsequent studies by others, however (GREENE and PECKHAM, 1951; NOVAK and MOHLER, 1953; ANTHONY and RODDICK, 1962; MARCUS, 1963), failed to confirm that association, and it now appears unlikely. — Hilus-cell tumors (MOHAMED *et al.*, 1978) and *Brenner tumors* (JOPP, 1965) have also been related to the development of endometrial carcinoma.

The rare patients in the childbearing period who develop endometrial carcinoma usually have abnormal ovaries; often there are signs and symptoms of the *Stein-Leventhal syndrome* (see Table 13; cf. also JAFARI *et al.*, 1978). It is necessary to point out, however, that the discoverors of this syndrome found no endometrial carcinomas in the first patients they described, and they then doubted whether the syndrome is always correctly diagnosed (LEVENTHAL, 1958). Certainly in all the combination-cases reported in the literature the authors have specified polycystic ovaries without corpora lutea, a state functionally equivalent to an unopposed estrogen effect. Clinically, all these young patients with endometrial carcinoma exhibit pronounced endocrine disturbances with obesity, diabetes mellitus, sterility and hirsutism. A corpus luteum is found only rarely. DOCKERTY *et al.* (1951) noted that the ovaries in 50 per cent of their cases were large and cystic. As to ovarian function, these young patients with endometrial carcinoma usually behave like women after the menopause. The simultaneous occurrence of pregnancy with endometrial carcinoma is extremely rare (SANDSTROM *et al.*, 1979).

It is worth mentioning that endometrial carcinoma develops more commonly in women with **cirrhosis of the liver** than in normal women (SPEERT, 1949), a fact that BREWER and FOLEY (1953) tried to disprove in their studies but could not. Presumably the damaged liver is unable to metabolize estrogen which then accumulates and overstimulates, unopposed by progesterone. GREENE (1941) reported endometrial carcinoma in rabbits that had damaged livers; he attributed the tumors to the reduced metabolism of estrogen.

The ovarian changes just described may result in an excessive or unopposed action of estrogen produced endogenously. We should like to compare with them the action of **exogenous estrogen.** A great many investigators have reported the development of an endometrial carcinoma after several years of estrogen therapy, in some instances after observing the development of all stages of hyperplasia that usually precede such a carcinoma (CORSCADEN and GUSBERG, 1947; NOVAK and RUTLEDGE, 1948; SPEERT, 1948 (in 12.5 per cent of his cases); RIEHM and STOLL, 1952; JENSEN and ØSTERGAARD, 1954; KOFLER, 1954; GUSBERG and HALL, 1961; BOUTSELIS *et al.*, 1963; LAUFER, 1968; CUTLER *et al.*, 1972, and numerous reports of single cases). RIEHM and STOLL (1952) were impressed by the histological peculiarities of these carcinomas, such as their formation of epithelial papillae in widely branching glandular lumina, their multicentric devel-

Table 13. Corpus carcinoma and the Stein-Leventhal syndrome

Author	Year	Number of patients with carcinoma under 40 years of age	Associated with Stein-Leventhal syndrome	
			number	per cent
SPEERT	1949	14	3	21
SOMMERS *et al.*	1949	16	4	25
DOCKERTY	1951	36	7	19
Total		66	14	21.2
		Number of patients with Stein-Leventhal syndrome	Associated with carcinoma	
			number	per cent
JACKSON, DOCKERTY	1957	43	16	37.2

opment, and their relatively high grade of differentiation. GUSBERG and HALL (1961) considered the glands of the adenomatous hyperplasias and carcinomas that develop after estrogen therapy to be so characteristic, they referred to an "estrogen carcinoma". From a study of our own cases of estrogen-induced carcinomas, which continue to increase in number almost weekly, we have been able to confirm all these histological peculiarities. The frequent occurrence of nodules of squamous epithelium in precancerous adenomatous hyperplasia is equivalent to the high percentage of adenoacanthomas that develop among "estrogen carcinomas" (cf. also ROBBOY and BRADLEY, 1979). Ultrastructurally, the endometrial cells of postmenopausal women receiving estrogen resemble those of adenocarcinoma in at least three features: accumulation of lipid droplets, irregular nuclei, and peri-nuclear whorls of microfibrils (AYCOCK and JOLLIE, 1979).

Large series of patient-collectives studied in the USA have disclosed that postmenopausal patients treated with estrogen have a six-fold greater risk for developing an endometrial carcinoma; those treated for more than five years have a fifteen-fold greater risk (ANTUNES *et al.*, 1979). In their studies SMITH *et al.* (1975), ZIEL and FINKLE (1975), BJERSING (1977), GREENWALD *et al.* (1977), HOOGERLAND *et al.* (1978) reached similar results. Giving gestagen with the estrogen does not increase the risk (GAMBRELL, 1977; GREENBLATT and BRYNER, 1977). Not only the duration of treatment but also the dosage prescribed is important for the development of carcinoma (GRAY *et al.*, 1977). The results of another study revealed that of ninety-four postmenopausal women developing endometrial carcinoma, 70% had received estrogens. In contrast, only 23% of a control-group of women of the same age without carcinomas had received estrogens (ZIEL and FINKLE, 1976). With sharp reduction in the dosage of estrogen the risk for endometrial carcinoma notably decreased (JICK *et al.*, 1979).

Recently several groups of investigators (LYON, 1975; SILVERBERG and MAROWSKI, 1975; KELLEY *et al.*, 1976; COHEN and DEPPE, 1977; REEVES and KAUFMANN, 1977; SILVERBERG *et al.*, 1977) have reported an increase in adenomatous hyperplasia and endometrial carcinoma in young women receiving oral contra-

ceptives with predominant estrogen effect. The increase is explained by the relative estrogen predominance during persistent artificial anovulation.

TWOMBLY *et al.* (1961) noted that their lean patients treated with estrogen quickly excreted it, whereas their obese patients retained the hormone. They attributed the higher incidence of carcinoma in the obese women to that retention.—In addition, a great many investigators have reported on precancerous adenomatous hyperplasias of the endometrium developing after estrogen therapy (GEIST *et al.*, 1941; KISTNER *et al.*, 1956; BLOOMFIELD, 1957; DOUGLAS and WEED, 1959; GUSBERG and KAPLAN, 1963).—Although the majority of the authors believed the endometrial carcinoma was related to the estrogen therapy, a few remained unconvinced of that relationship (LARSON, 1954; DIBBELT *et al.*, 1962). These differences are due in part to geographical factors. In the United States estrogen has been prescribed during the climacterium and even for young women for a much longer time than in Germany. Consequently, in the larger series of American patients treated with estrogen the relationship—estrogen:endometrial carcinoma—became apparent sooner. Furthermore, the duration of estrogen therapy proved to be much more important than the height of the single doses (CORSCADEN and GUSBERG, 1947; MÜHLBOCK, 1959, 1963; JENSEN, 1963), since most of the carcinomas developed after prolonged therapy with low doses of estrogen.

After estrogen therapy is discontinued a high-grade adenomatous hyperplasia may completely regress spontaneously (NOVAK and RUTLEDGE, 1948; OSTERGAARD, 1974), whereas adenomatous hyperplasia due to excessive endogenous estrogen will require prolonged therapy with high doses of gestagens before it regresses. KISTNER (1959) reported that progesterone therapy successfully caused two adenocarcinomas in situ to disappear.

A certain percentage of patients with endometrial carcinoma may give a history of having received **x-irradiation** many years before, usually for benign uterine leiomyomata or endometrial hyperplasias (NORRIS and BEHNEY, 1936; COSTOLOW, 1941; SCHEFFEY, 1942; CORSCADEN *et al.*, 1946; SMITH and BOWDEN, 1948; HERTIG and SOMMERS, 1949; SPEERT and PEIGHTAL, 1949; MONTGOMERY *et al.*, 1952; BARR and CHARTERIS, 1955; TURNBULL, 1956; PENTECOST and BRACK, 1959; REICHER and PHILLIPS, 1961; DIBBELT *et al.*, 1962; BOUTSELIS *et al.*, 1963; WALL *et al.*, 1967). When the patients with endometrial carcinoma of all these authors are grouped and analyzed, 7.2 per cent are found to have had X-ray therapy to the pelvis, a percentage not significantly greater than that of control patients without carcinomas.

DIBBELT *et al.*, found among their patients with carcinoma that 7.9 per cent had had previous X-ray therapy of the small pelvis, whereas in their series of control patients 5.8 per cent had received such therapy. Several other investigators were equally as cautious in relating X-ray therapy with the subsequent development of carcinoma (KOCH, 1949; COPELAND *et al.*, 1957; HOFMANN, 1960; HUBER, 1960; NIELSEN, 1960; KEPP, 1961; BRINKLEY *et al.*, 1963; SHUTE, 1963). By X-irradiating the ovaries of animals, HUSSY and WALLART (1915) produced follicular degeneration and hyperplasia of the theca cells with a definitely increased estrogen activity. FURTH and BUTTERWORTH (1936) were the first to describe the development of granulosa-cell tumors in mice by irradiating their ovaries with X-rays.

Women who have had their ovaries removed rarely develop endometrial carcinoma. Nevertheless, in the literature there are twenty-eight case-studies of castrated women in whom endometrial carcinomas ultimately developed (MEYER, 1923: 1; SMITH, 1941: 3; RANDALL *et al.*, 1951: 4; CIANFRANI, 1955: 8; BROMBERG *et al.*, 1959: 1; HENRIKSEN, 1960: 2; HOFMEISTER and VONDRAK, 1970: 9), and I have observed another myself. According to the clinical records, at least 4

of these patients developed their carcinoma after many years of estrogen replacement therapy. In the other patients reported, estrogen most probably was compensatorily produced by the adrenal cortices, as has been frequently assumed in women after the menopause (NOVAK and RICHARDSON, 1941; RANDALL *et al.*, 1957; SCULLY, 1953; SMITH *et al.*, 1959) and as was demonstrated biochemically (HUSSLEIN, 1950; KASE and COHN, 1967). NISSEN-MEYER and SVERDRUP (1961) detected large amounts of estrogen in the urine of castrated women. Since oophorectomy will bring about a hypersecretion of LH, leading thus to a compensatory formation of estrogen, the development of an endometrial carcinoma in castrated women speaks for a relationship between carcinoma and hyperestrogenism rather than against it. Further, endometrial carcinomas developing after unilateral oophorectomy are becoming more common, particularly in women under forty years of age (KEMPSON and POKORNY, 1968). WILKINSON *et al.* (1973) reported on a patient with ovarian dysgenesis (Turner's syndrom) who received stilbestrol therapy for 9 years and developed an adenocarcinoma of the endometrium. In a search of the literature they found the reports of four similar cases and therefore interpreted the apparently interrelated train of events as an iatrogenic model for the induction of endometrial carcinoma. MCCARTY *et al.* (1978) cited 13 comparable cases and described one of their own patients, who developed an endometrial carcinoma after 31 years of estrogen therapy. VAN CAMPENHOUT *et al.* (1980) collected 18 similar cases.

Biochemical measurements of urine have indicated that women with corpus carcinomas have **persistently increased levels of estrogen** (PINCUS and GRAUBARD, 1940), also in blood plasma (ALEEM et al., 1976). In addition, the vaginal epithelium of a high percent of postmenopausal women with corpus carcinoma shows a distinct estrogen effect (HERRELL, 1939; AYRE and BAULD, 1946; LIMBURG, 1951; NOVAK and MOHLER, 1953; WIED, 1953; LIU, 1955; BERG and DURFEE, 1958; STOLL and PECORARI, 1962; CHANG and CRAIG, 1963; CHARLES *et al.*, 1965; RITCHIE, 1965; CREPET and NUOVO, 1967; DE WAARD and OETTLE, 1967). According to HERTIG (1957), women with senile vaginitis never develop a corpus carcinoma. Some authors (e.g., CRAMER and WILDNER, 1953) were unable to detect an increased level of estrogen in patients with endometrial carcinoma. Other investigators have reported an increase in the LH secretion in their patients with corpus carcinoma (SHERMAN and WOOLF, 1959; VARGA and HENRIKSEN, 1963), or an increase in androgens (WITTLINGER *et al.*, 1975). These discrepancies, however, are only apparent. We know that androgenic substances are readily metabolized into estrogenic substances. HAUSKNECHT and GUSBERG (1973) found a significantly higher conversion rate of Δ^4-androstenedione to estrone in patients with endometrial cancer than in normal postmenopausal patients. Hence, the notable postmenopausal estrogen probably is estrone, and androstenedione its steroid precursor. In addition, androgens have been shown to activate the transfer of the estrogen receptor to the nucleus (ROCHEFORT *et al.*, 1972). The concentration of estrogen receptor in differenciated endometrial carcinoma is very high as compared with that in normal endometrium (cf. p. 197).

It seems only logical to relate the endometrial *foam cells* with the persistently elevated levels of estrogen. Earlier workers who saw and described these cells were uncertain about their origin; they never could demonstrate evidence of

a hypercholesterolemia or an inflammatory process. Many endometrial carcinomas with foam cells have developed in patients who had received estrogen therapy for years; in one patient an ovary had once been removed. I have in my collection of endometrial carcinomas one tumor whose entire stroma had undergone change into foam cells; the patient had been treated with stilbestrol for twenty years. EPSTEIN (1976) noted that the foam cells developing in prostatic carcinomas after estrogen therapy resembled those arising in the endometrium. Since the stromal cells of the endometrial carcinoma electron-microscopically reveal an extensive well-developed ergastoplasm (WESSEL, 1965), they are without doubt functionally active. BLACK *et al.* (1941) found fat droplets in almost all stromal cells of the endometrium of a castrated patient treated with estrogen for six years. The normal endometrium of the menstural cycle is free of such accumulations of fat. In contrast, the greatest number of foam cells (in over 50 per cent of the cases) are found in adenomatous hyperplasias and fewer (30 per cent) in glandular-cystic hyperplasias. Accordingly, it seemed logical to assume that the foam cells represented a reaction of the endometrial stroma to an unremittingly high, unopposed estrogen, be its source endogenous or exogenous. Previous studies suggested the foam cells contained cholesterol, which is known to be a precursor or byproduct of estrogen-synthesis (INHOFFEN, 1940; WERBIN and LEROY, 1954; DORFMAN, 1957). The endometrial stromal cells are known to be subtle indicators of hormonal stimuli. The transformation of the stromal cells into foam cells resembles their change into decidual cells. Both of these processes of conversion first take place in the same regions of the stroma: in the superficial and well-vascularized regions. The one change excludes the other, however. When decidual cells and endometrial granulocytes develop, no foam cells appear; when the foam cells develop, no decidual cells or granulocytes form. The number of foam cells diminishes as the malignancy advances. Even in an early carcinoma decrease from the adenomatous hyperplasia is evident. Of the carcinomas, the adenoacanthoma contains the most foam cells (see Fig. 92).

Table 14 provides a survey of the endocrine disturbances associated with endometrial hyperplasias and carcinoma and relates these disturbances with the duration of endogenous or exogenous hyperestrogenism. I took into account only the glandular-cystic hyperplasias occurring after the menopause, since it is only these that are important as potential precursors of carcinoma (NOVAK, 1956). As compared with the controls, the carcinoma and all forms of hyperplasia disclose very similar incidences of endocrine disturbances and hyperestrogenism. If the percentages for the various sources of hyperestrogenism listed under carcinoma are added, one obtains almost 100 per cent, indicating that in the great majority of endometrial carcinomas an unopposed estrogen-effect is to be expected. Consequently, it seems more likely that under the same hormonal stimulus a sequence proceeds from the glandular-cystic hyperplasia to adenomatous hyperplasia and from it to adenocarcinoma in situ and ultimately to carcinoma; these pathological conditions should be looked upon as merely various ways in which the same persistent hormonal disturbance can express itself (see GORE and HERTIG, 1966; GUSBERG, 1967).

Some authors (HOFFBAUER, 1931; MOSS, 1946; THIESSEN, 1952; WAY, 1954;

Table 14. Relationships between endocrine abnormalities or endogenous and exogenous estrogen and endometrial carcinoma and its precursors

	Average age in years	Nulli-para (% with)	Obese patients (% with)	Diabetic patients (% with)	Patients with ovarian changes			Patients given therapy	
					feminizing tumors (% with)	stromal hyperplasia (% with)	Stein-Leventhal (% with)	estrogen (% with)	X-irradiation (% with)
Glandular-cystic Hyperplasia[a]	after the menopause	36.0	52.0	16.0	10 – 92	60.0		21.5	
Adenomatous hyperplasia[b]	45 – 50	34.5	41.6	3.7	4.0			16.0	
Adeno-carcinoma in situ[c]	49	33.0	54.0		5.0	42.5		6.3	15.6
Adeno-carcinoma[d]	57.5	33.9	46.0	10.9	total: 1.7 postmenopausal: 2.9	72.2	total: 4.1 premenopausal: 21.2	13.2	7.2
Control patients	equivalent	15.4	25.9	2.6	0.6	39.2	0.07		5.8

[a] After KOTTMEIER (1947), DHOM (1952), NOVAK (1956), FROMM (1959) (286 Cases).
[b] After GARNET (1958), GUSBERG and KAPLAN (1963) (203 Cases).
[c] After HERTIG *et al.* (1949) (64 Cases).
[d] Compiled from the literature, numbering about 12,000 cases (see DALLENBACH-HELLWEG, 1964; further references: BENJAMIN and ROMNEY, 1964; COUREY and GRAHAM, 1964; TWEEDDALE *et al.*, 1964; CHARLES, 1965; LYNCH *et al.*, 1966; WYNDER *et al.*, 1966; WALL *et al.*, 1967; DUNN *et al.*, 1968; GEISLER and GIBBS, 1968; PFLEIDERER, 1968).

SOMMERS and MEISSNER, 1957; GARNET, 1958; PRINTER, 1963; WYNDER *et al.*, 1966) have tried to relate the hyperestrogenism seen with endometrial carcinoma and the associated endocrine disorders to a **disturbance of the pituitary gland,** providing thereby a single explanation for all the signs and symptoms. It is certainly conceivable, for example, that a disturbance in the secretion of LH would depress ovulation and thus stimulate a secretion of estrogen. Often the adrenals are also functionally abnormal, as evidenced by hypersecretion of the cortex (KAISER, 1969). It seems so difficult to decide, however, what is primary and what is secondary in this complex endocrine disorder that one must be careful about postulating such dysfunction of the pituitary. Hyperestrogenism, on the other hand, seems to be a fundamental factor in the induction of endometrial carcinoma. The height of the estrogen level is much less important, however, than the constancy of its secretion. Certainly constitutional factors dispose to unopposed production of endogenous estrogen as well as to diabetes mellitus, hypertension, and obesity. An endocrine disturbance due to constitutional factors explains the frequent inherited disposition for endometrial carcinoma (LYNCH *et al.*, 1966, 1967). According to BULLOUGH (1955) estrogen increases the permeability of the cell membrane for glucose. On the other hand, in obesity estrogen

seems to be stored in adipose tissue (TWOMBLY *et al.*, 1967). Especially after the menopause and with obesity more estrogen is formed from androgen, as the conversion-rate of androstendione into estrone increases (SCHINDLER, 1977; SIITERI, 1978). When patients in the menopause develop a bloody discharge while on estrogen therapy, a curettage discloses in a high percentage of them a precancerous or carcinomatous endometrium (BARTER *et al.*, 1968).

The foregoing considerations lead us to the difficult and much-discussed question about **the importance of estrogen for the development of endometrial carcinoma.** The action of estrogen on the endometrium fundamentally is to induce regeneration to restore the tissue lost with menstruation. During a normal menstrual cycle that action is held in check by progesterone (which causes differentiation) and relaxin (which causes dissolution of the connective tissue); regeneration is maintained within physiological bounds. A persistent stimulation by unopposed estrogen over many years or even decades may, on the other hand, through the unremitting proliferation of the endometrium, greatly facilitate a spontaneous mutation or one caused by a carcinogen (BAUER, 1963), especially in a genetically susceptible patient. As HAMPERL pointed out (1956), carcinogens act best in proliferating tissues. BÜCHNER (1961) spoke of the increase of accidental mutation accompanying an intensified doubling of the DNA. Accordingly, estrogen was regarded as a limited carcinogen which acts only on specific organs (BUTENANDT, 1949, 1952; DONTENWILL, 1961, 1965, 1966; WAGNER *et al.*, 1967) or as a syncarcinogen (BAUER, 1963; KRUSCHWITZ, 1967). The aphorism by IGLESIAS (1965): "either I do differentiate and I die, or I do not differentiate and I kill", seems to apply especially well to the endometrial cells still under hormonal control. May estrogens alone under certain circumstances act as carcinogens? Although that question in general remains unanswered, at least for synthetic estrogens (stilbestrol) it seems they can, as the vaginal carcinomas they induce (prenatally) in young women prove. It is well known that natural estrogens can induce malignant tumors in experimental animals. We should also recall that estrogens directly influence the synthesis of DNA and the process of mitosis. Consequently, we need to ask, whether estrogens might not possess a limited carcinogenic effect modified by circumstances, such as the lack of an opposing effect from progesterone. Otherwise, one will have to assume that ubiquitous carcinogens exist that can act on the endometrium but need estrogen stimulation (a cocarcinogen) to become fixed. For the patient such a cocarcinogenic action of estrogen would be just as important as a possible carcinogenic action. This discussion emphasizes once again how imperative it is that we learn how estrogen acts on its target cell.

That the effect of estrogen depends on genetic disposition explains why the individual response to a persistent secretion of unopposed estrogen is so diverse (BÜNGELER and DONTENWILL, 1959). In women, excessive stimulation of the endometrium by estrogen incites the stroma and epithelium to proliferate, the type and degree of proliferation, however, varies from patient to patient. Papillary growths or squamous metaplasia may develop (STOHR, 1942), and in some women even myomata or diffuse myometrial hyperplasia or adenomyosis may occur. Only a few of these changes may arise or they may all appear together. The type of gland (for example, glands with papillae, or those lined either by tall

cylindrical cells or by low cuboidal cells, or by stratified epithelium, or by secreting cells, and so forth) that evolves at the onset of the a patient's hyperplasia will persist through all subsequent stages and usually will still be seen in the carcinoma if that ultimately develops (GRUNER, 1942; BEHRENS, 1956). Experimentally, a wide spectrum of various types of benign and malignant tumors have been produced in many species of animals with estrogens (for compilation refer to TAYLOR, 1938; GARDNER, 1939; ALLEN, 1942; TAYLOR, 1944; LIPSCHÜTZ, 1950; GARDNER *et al.*, 1959; TAKI and IIJIMA, 1963; DALLENBACH, 1971).

The histological picture of the endometrium is perhaps the most precise indicator for evaluating the intensity of estrogen effect; it surpasses by far the information obtained by biochemical determinations of either urine or blood. Fig. 96a provides a schematic summary of the importance of estrogen in the development of endometrial carcinoma.

Glandular-cystic hyperplasia is the first response of the endometrium to an unopposed secretion of estrogen. Since the action of estrogen before the menopause can be blocked by the occasional secretion of progesterone, hyperplasia seldom progresses during that time. Depending on the levels of the two hormones, the histological picture may vary, either remaining unchanged or exhibiting variable secretory changes, proliferations of cystic glands, or regression. On the basis of our present knowledge it seems logical to classify glandular-cystic hyperplasia as a *facultative precancerous state* (Tab. 11). The same holds true for circumscribed hyperplasias and proliferating polyps, as well as for irregular proliferations, since these may at times skip a glandular-cystic stage and progress directly into an adenomatous hyperplasia.

The *adenomatous hyperplasia* is the first histological sign of a persistent unopposed effect of estrogen. It usually develops from the glandular-cystic hyperplasia slowly over a few years if the estrogen stimulus continues unabated; through the unremitting secretion of estrogen the glands are continuously driven to proliferate more and more. Usually the progression to adenomatous hyperplasia comes about first after the menopause; if it occurs before the menopause then only during a protracted period of anovulation. The level at which estrogen secretion continues determines what happens to the adenomatous hyperplasia. If the secretion of estrogen wanes, then the hyperplasia may regress. If the estrogen secretion remains high and the endometrium is left untreated, then the glands of the adenomatous hyperplasia continue to proliferate and within a few years become carcinomatous. Consequently, we should look upon adenomatous hyperplasia as an *obligatory precancerous state*, depending however on certain circumstances. The small percentage of adenomatous hyperplasias that regress are almost always those induced by exogenous estrogens, whereby it may be possible to stop estrogen therapy and further stimulation in time. With endogenous hyperestrogenism, however, the state of hyperplasia is usually refractory. We should also include in this group the localized forms of adenomatous hyperplasia and adenomatous polyps, although these may at times be spontaneously shed and totally discharged. The same pertains for juvenile adenomatous hyperplasia: If spontaneous ovulations fail to occur and if left ignored and untreated, it will inevitably progress to carcinoma.

The advance to irreversibility in this progression is morphologically detectable

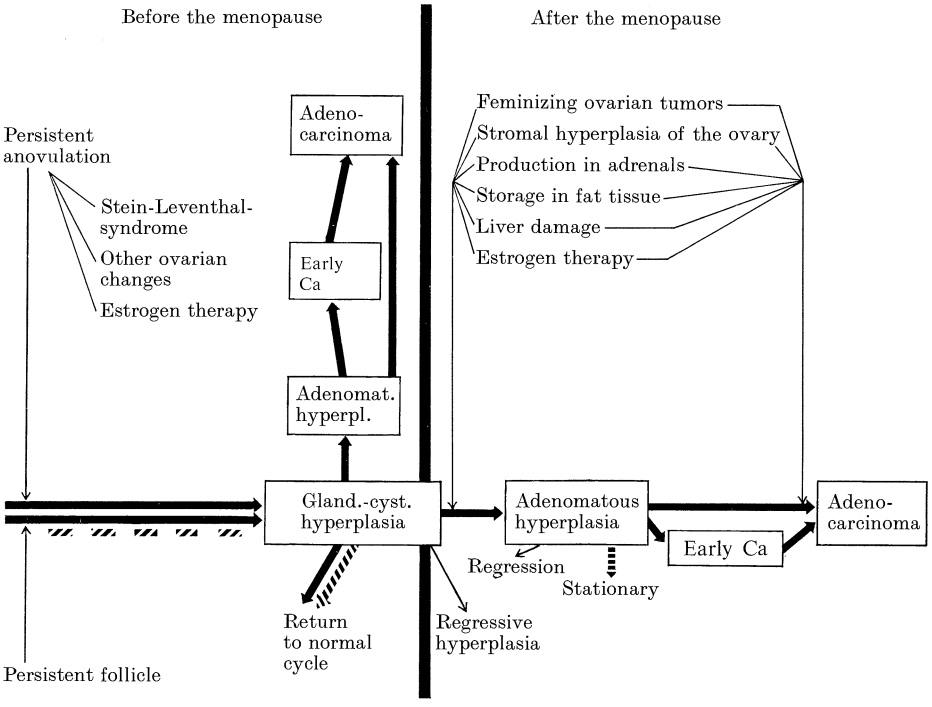


Fig. 96a. Development of endometrial carcinoma from its precursors through the action of estrogen. The heavy black arrow = estrogen; the broken arrow before the menopause = progesterone

in only some of the cases, when *an early carcinoma* proceeds the development of a frankly invasive carcinoma. The decrease in the cytoplasmic RNA observed in such regions is equivalent to that frequently described in early carcinomas of other locations (EMMELOT and BENEDETTI, 1960; BERNHARD, 1961; BÜCHNER *et al.*, 1963). On the other hand, the acceleration in growth rate at the onset of malignancy may occur without any changes in cellular structure and thus elude histological detection (as for example, in the carcinoma of the prostate; HAMPERL, 1952, 1957). Such concealed transition explains why it often is so difficult to distinguish an adenomatous hyperplasia from a beginning adenocarcinoma. Since adenomatous hyperplasia often proves difficult to evaluate histologically, it is highly advisable to gather information on the source and degree of the estrogen stimulation and on associated clinical signs and symptoms. In some cases of adenomatous hyperplasia the presence of foam cells in the endometrial stroma will be of prognostic importance, since they indicate that the estrogen stimulus has been intense for a long time.

An endometrial carcinoma may still be under the influence of estrogen, but it need not be. The repeated observation that some patients with endometrial carcinoma do not have elevated levels of estrogen (RAURAMO *et al.*, 1964) can

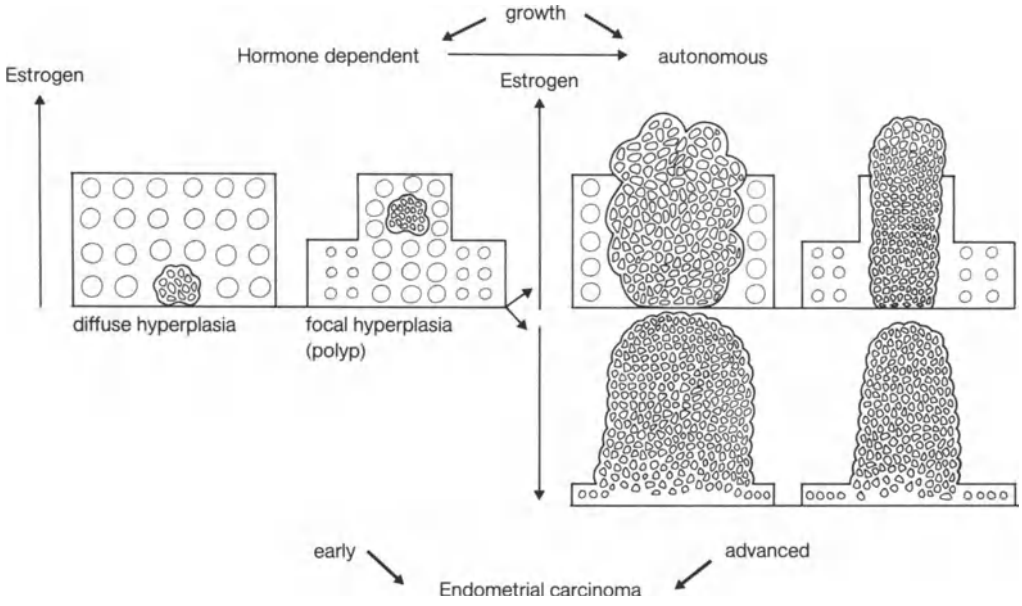


Fig. 96 b. Schema depicting how the level and persistence of estrogen stimulation influence the endometrium surrounding early endometrial carcinomas and later advanced stages

be explained by a decline in estrogen secretion after the carcinoma developed. It can also be explained by the possibility, that the cells of the endometrial carcinoma, an estrogen target tissue, have a much greater affinity for estrogen than do the carrier proteins of the plasma. Thereby, the endometrial carcinoma would take up, metabolize, or store in foam cells most of the estrogen available. During the preinvasive phase of endometrial carcinoma the plasma levels of estrogen are always high (ALEEM *et al.*, 1976). When the endometrial carcinoma begins to grow autonomously, the high level of estrogenic stimulation may either persist or decrease. If the level remains high, then the adjacent noncarcinogenic endometrium continues to be hyperplastic. If the level decreases, the adjacent noncarcinogenic endometrium becomes atrophic, giving the false impression that the carcinoma has arisen in an atrophic endometrium (see Fig. 96 b).

Progesterone Treatment of Endometrial Carcinoma: The demonstration that precancerous and carcinomatous growths may be hormone-dependent and that gestagens inhibit mitoses (KAISER, 1959; NORDQUIST, 1964) and induce regression of endometrial carcinoma (VARGA and HENRIKSEN, 1961) led to the clinical use of progesterone for treating adenomatous hyperplasia and inoperable carcinoma of the endometrium (THIESSEN, 1956; KISTNER, 1959; KISTNER and SMITH, 1960; KELLEY and BAKER, 1961, 1965; KISTNER *et al.*, 1965). KOTTMEIER (1962) was able to improve the condition of nine out of eleven women suffering from corpus carcinoma with pulmonary metastases by giving them daily 0.2 mg of progesterone (later 150 mg per week). In four patients the pulmonary metastases disappeared.

BERGSJÖ (1965), FRICK (1965) and MUSSEY and MALKASIAN (1966) treated their patients, who also had metastases from their endometrial cancers, with considerably larger doses of progesterone (from 200 mg three times a week to 1.5 g to 2 g a week) and induced secretory changes in the tumors. In 25 per cent of these patients the pulmonary metastases regressed. INGERSOLL (1965) also observed a regression of pulmonary and hepatic metastases in 25 per cent of his patients with stage IV endometrial carcinoma. In other series totalling about 400 patients who had received progesterone therapy for their endometrial carcinomas, usually as hydroxyprogesterone caproate (="Delalutin"), or medroxyprogesterone acetate (="Depo-Provera"), clinical improvement with regression of the primary tumor and metastases (especially the pulmonary and osseous) was reported in about one-third of the patients after one to three or more months of treatment (WENTZ, 1964; ANDERSON, 1965; KELLEY and BAKER, 1965; BONTE *et al.*, 1966; VARGA and HENRIKSEN, 1965; SHERMAN, 1966; WATERMAN and BENSON, 1967; KENNEDY, 1968; PECK and BOYES, 1969; REIFENSTEIN, 1971; PIVER *et al.*, 1980). The longer the interval between primary gestagen therapy and recurrence, the better the response to the drug, a significant correlation because of the many diverse factors involved.

Patients responding survived four times as long as the nonresponders. The degree of tumor differentiation proved important: about 50% of mature adenocarcinomas responded to gestagen therapy (BOQUOI and KREUZER, 1973) whereas only about 15% of poorly differentiated did (KOHORN, 1976). MARTZ (1968) recommended giving 500 mg "Proluton" two times a week for the treatment of pulmonary metastases but 2–5 g a week for metastases in the small pelvis and bones. Since there are no serious side-effects with the larger doses, these can be administered without concern.

We recommend treating patients with adenocarcinomas in stages III and IV with continuous gestagen at a dose of 2 g per week for as long as they live. Patients with tumors in stage I should receive that treatment for one year. If the patient cannot be operated upon and her adenocarcinoma is well differentiated, one may consider therapy alone with gestagens. The success of that therapy can be followed with periodic curettages but must be maintained until the endometrium becomes atrophic. If treatment is discontinued prematurely, for example at the stage of arrested secretion, the tumor cells may recover their growth potentialities. Preoperative therapy with gestagens is also a possibility to be contemplated, especially when considerable time is required to prepare the patient for her operation. Basically, any gestagen preparation may be used. Because of their greater gestagen potency, the 19-nortestosterone derivatives are more efficacious than those of progesterone (GAMBRELL, 1977, 1978).

It has been known from experience for some time, that well-differentiated endometrial carcinomas respond much better to gestagen therapy than do the poorly differentiated carcinomas. The modern techniques for measuring *estrogen and progesterone receptors* have confirmed that experience and explained why it is true. The higher the degree of differentiation of a carcinoma, the more estrogen receptor its cells produce (EVANS and HÄHNEL, 1977, POLLOW *et al.*, 1975, POLLOW and BOQUOI, 1976) whereas at the same time the content of

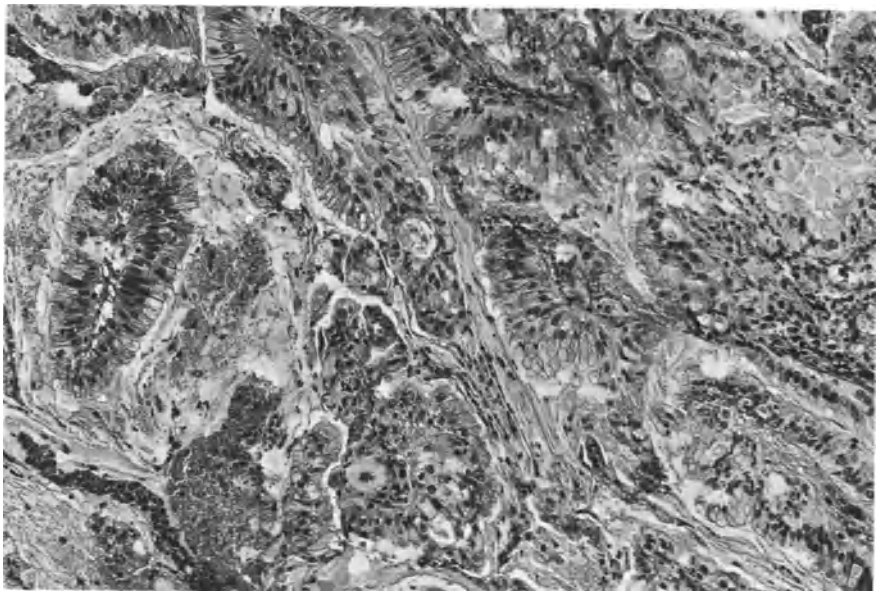


Fig. 97. Adenocarcinoma after several weeks of treatment with gestagens. Secretory change of the glandular epithelium; vacuoles forming in the basal parts of the cells; the nuclei have become rounded

progesterone receptors may be high (McCarty *et al.,* 1979) or low (Tseng *et al.,* 1977), but after treating with the antiestrogen agent, tamoxifen, sharply increase. Therapy with progesterone inactivates the progesterone receptors (Bjersing, 1977, Rodriquez *et al.,* 1979). The more poorly differentiated the carcinoma becomes, the greater the nuclear receptors for progesterone decrease (Young *et al.,* 1976). In contrast, the concentration of nuclear receptors for estrogen remains constant in all carcinomas, regardless of the degree of differentiation (Pollow *et al.,* 1977). Carcinomas without receptors are refractory to hormone therapy. From their studies McCarty *et al.* (1979) point out that the histologic grading of endometrial carcinoma correlates with its levels of both estrogen and progesterone receptors, which often are considerably above those seen in normally cycling endometria. Receptor analysis may therefore provide the best criterion for selecting therapy for endometrial carcinoma, and may refine the prognostic value of histologic grading.

Histophotometric measurements of carcinomatous tissues or normal tissues cultured in vitro revealed a distinct decrease in the synthesis of DNA and RNA after treatment with progesterone (Nordquist 1969, 1970; Hustin 1975, 1976; Simon and Hölzel, 1979; Ferenczy, 1980). Their sets of chromosomes also became diploid and euploid. These results mean that progesterone acts directly on the DNA synthesis of cells of endometrial carcinoma. At the same time, progesterone may exert its antiestrogenic effect by preventing estrogen

from binding to its receptor. After gestagen therapy, the numerous nuclear inclusions, cytoplasmic vacuoles and lysosomes with disrupted membranes seen in electron-microscopic studies signify cellular injury (SIRTORI, 1969). Three weeks after starting progesterone therapy the activity of alkaline phosphatase histochemically decreases (MOE, 1972), whereas in only mature carcinomas the activity of 17β-hydroxysteroid-dehydrogenase rises sharply (POLLOW *et al.*, 1975), paralleling the increase in content of progesterone receptors (POLLOW and BOQUOI, 1976).

The histological changes produced in well-differentiated endometrial carcinomas by gestagen therapy resemble those that develop during a normal secretory phase. As early as three days after starting therapy secretory vacuoles appear in the glandular cells of the carcinoma (Fig. 97), the pseudostratified arrangement of their nuclei recedes, and the number of mitoses decreases. As therapy continues, the production of glycogen and mucus by the glandular epithelium increases (cf. JOHN *et al.*, 1974). Finally, and characteristic of progesterone therapy, are the changes that develop in the non-carcinomatous endometrium. (cf. S. 221). – The intrauterine administration of synthetic gestagens has the same effect on the carcinoma cells, as studies of uteri removed after such therapy proved (KISTNER *et al.*, 1965; HUSTIN, 1970).

Besides these histologically and biochemically detectable effects of progesterone directly on the endometrial carcinoma (HACKL, 1968), progesterone most probably exerts an inhibitory action on the hypophysis since it depresses the secretion of LH.

Treatment with *Clomiphene* (200 mg daily for seven months) led to similar favorable results (WALL *et al.*, 1964, 1965). NORDQVIST (1969, 1970) measured the synthesis of DNA and RNA by endometrial carcinoma in tissue-culture and was able to demonstrate a reduction in the synthesis of both after he had added progesterone. He therefore postulated that progesterone acted directly on the DNA of the nuclei of the tumor cells.

The resistance of poorly differentiated carcinomas to progesterone therapy might develop because the cells of the carcinoma have lost their dependency on estrogen long before, after which time the secretion of estrogen by the patient might have ceased. Since estrogen is needed to stimulate the target cells to produce progesterone receptors (see p. 46), progesterone therapy may be effectual in these patients if preceded by estrogen or if both hormones are given together (see also COLLINS, 1972).

The analysis we have just made of the problems involved in the pathogenesis of endometrial carcinoma enables us to understand how rational gestagen therapy is for all forms of estrogen-induced hyperplasias after the menopause, and how such therapy serves as a prophylaxis against the development of endometrial carcinoma (see also KAISER, 1969). Even in the precancerous hyperplasias, gestagen therapy must be continued over many months, until complete fibrous atrophy of the endometrium has been produced to avoid recurrences (see also EICHNER and ABELLERA, 1971). According to GUSBERG (1976) all risk patients should be considered here, in whom an adenomatous hyperplasia might be detected early in a suction biopsy performed as an outpatient procedure.

For alleviating climacteric complaints many authors advocate treating with

estrogens and gestagens together (WHITEHEAD *et al.*, 1977; GAMBRELL, 1978, HAMMOND *et al.*, 1979) Ninety-four per cent of all patients receiving estrogen alone (1.25 mg daily) developed endometrial hyperplasia, whereas when 10 mg of medroxyprogesterone were added daily during the fourth week, only 6% developed the hyperplasia (cited from GAMBRELL, 1977). As the best prophylaxis to prevent the development of endometrial carcinoma, GAMBRELL (1978) recommends giving all postmenopausal women a test dose of gestagen, whether they are taking estrogens or not. If the patient experiences a withdrawal bleeding then that means she has a hyperproliferative endometrium and should be treated further cyclically with gestagens until the bleeding ceases. If the patient experiences no withdrawal bleeding, her endometrium is either refractory, resting or atrophic, and an endometrial carcinoma cannot develop. In their four year study, GAMBRELL *et al.* (1980) found that their postmenopausal patients treated with estrogen and progesterone had a significantly lower incidence of endometrial carcinoma than their patients receiving estrogens alone or even untreated patients. Their results are easier to understand when we recall that about 25 per cent of all postmenopausal women continue to produce fairly high levels of estrogen after their menopause.

After **X-ray therapy** the endometrial carcinoma may lose its glandular character. The secretions become inspissated and giant cells may form (SHEEHAN and SCHMITZ, 1950). In contrast to their response to gestagen therapy, the well differentiated adenocarcinomas are usually resistant to irradiation, whereas the poorly differentiated or socalled undifferentiated types respond to it fairly well. It is therefore very important to correctly classify the carcinoma as to histological type, since the treatment of choice depends on its proper classification.

c) Sarcoma of the Endometrium

The sarcomas that develop in the uterus almost always involve the endometrium, either primarily or secondarily, and depending on their sites of origin, may be divided into three groups: the endometrial sarcoma, the endometrial mixed mesenchymal tumor, and the leiomyosarcoma. In general the ratio of uterine sarcomas to uterine carcinomas (endometrial and cervical) is about 1:50. The sarcomas account for 2.04 – 6.33 per cent of all malignant tumors of the uterus (RANDALL, 1943; WEISBROT and JANOVSKI, 1963). The leiomyosarcoma is about three times more common than the endometrial sarcoma (BOUTSELIS and ULLERY, 1962; BÖHM and STECH, 1966; BARTSICH *et al.*, 1968). Generally, the sarcomas appear in the fifth decade of life (RANDALL, 1943; NORRIS and TAYLOR, 1966; WILDNER and KLEIN, 1967); the patients with leiomyosarcoma are somewhat younger than those with the other types of sarcoma.

The **endometrial stromal sarcoma,** which usually arises from the stromal cells of the fundic endometrium, grows into the uterine cavity as a soft, polypoid or lobulated and knobby mass. At times it may enlarge the uterus to the size of a 6 month pregnancy. On the other hand, the endometrial stromal sarcoma invades the myometrium and its vessels early (in 75 per cent of the cases), and may extend through the serosa to involve either directly or by the pelvic veins

the neighboring organs and tissues. The surface of the freshly sectioned tumor is yellow, flecked by numerous small hemorrhages and cyst-like clefts. Necrotic portions may be discharged vaginally.

Histologically under low magnification the most striking feature is the disproportion between glands and stroma (Fig. 98a). The glands are unusually sparse and often absent in large regions of the stroma, but in other parts may be pushed together in small, irregular groups. Under higher magnification the hypercellularity of the stroma is readily apparent, the densely packed cells possessing large nuclei, some of which are hypochromatic or undergoing mitosis (Fig. 98b). The cells normally are fusiform but when transected they appear round. Ultrastructurally they resemble stromal cells of the early proliferative phase (KOMOROWSKI *et al.,* 1970; AKHTAR *et al.,* 1975); their cytoplasm may be either scanty or abundant, depending upon their degree of differentiation, but generally appears immature, containing only a sparsely developed rough endoplasmic reticulum (BÖCKER and STEGNER, 1975). Only rarely do these neoplastic stromal cells differentiate along the two lines open to normal stromal cells. For example, BÖHM and STECH (1966) observed decidual-like changes in the sarcomatous cells, and KAZZAZ (1975) described a granulocytic sarcoma in a 69 year old woman. The pleomorphic cells of her tumor had round, hyperchromatic nuclei and in their cytoplasm disclosed strongly birefringent, phloxinophilic granules. Histochemically, these cells corresponded to endometrial granulocytes. Independently, BÖCKER (1980) recently published electron-microscopic studies of neoplastic endometrial granulocytes and suggested these represented a special form of differentiation of endometrial stromal sarcoma. Reticulum stains often reveal that each cell is enmeshed in a net of fibers. Other intercellular substances are lacking. Small capillaries are abundant. Generally the uniformity of the tumor cells is striking. In rare instances, however, the polymorphism of the nuclei may be pronounced; giant cells containing multiple nuclei or large bizarre forms then are often present (Fig. 99). The nuclear polymorphism may be so slight, however, that one has difficulty in recognizing the sarcomatous stromal cells as such and in not confusing them with hormonally-stimulated stromal cells (OBER and JASON, 1953). In such cases a beginning endometrial stromal sarcoma is often either easily overlooked or is erroneously diagnosed. An abnormally cellular, sarcoma-like stroma is no proof of sarcoma as long as the glands are evenly distributed. On the other hand, if abnormal stromal cells are found penetrating the myometrium, as they often do early, then that invasive growth alone makes it easier to recognize the tumor.

The endometrial stromal sarcoma almost always *develops* from a stromal hyperplasia, which is equally as rare (see p. 128) and histologically similar except it does not invade. Thus, stromal hyperplasia may be referred to as a "sarcoma in situ". It may prove difficult to differentiate stromal hyperplasia from stromal sarcoma (SYMMONDS *et al.,* 1957). Only a few investigators have assumed that a sarcoma could develop from a glandular-cystic hyperplasia (HUGHESDON and COCKS, 1955), in which the stroma had presumably undergone intense circumscribed hyperplasia. The association of a uterine sarcoma with a pregnancy has been described several times (STUTZER, 1947; BRUCE and DICK, 1956; TAYLOR, 1958). The tumor may simulate a placenta praevia.

Endometrial stromal sarcoma often *metastasizes* early, not only out into the peritoneal cavity but also by way of the blood vessels and lymphatics into the liver and lungs (WHEELOCK and STRAND, 1953); metastases to the bones (FARROW *et al.*, 1968) or heart (STEELE *et al.*, 1968) are rare.

According to most authors the *prognosis* is extremely bad (see KOSS *et al.*, 1965; WHITE *et al.*, 1965; GÜNTHER, 1967); MCDONALD *et al.* (1940) as well as BOUTSELIS and ULLERY (1962) state that even with radical surgery only about 20 per cent of the patients survive more than five to six years. NORRIS and TAYLOR (1966) on the other hand give somewhat higher survival-rates.

The **malignant mixed mesenchymal tumors** (AARO *et al.*, 1966; NORRIS *et al.*, 1966; RACHMANINOFF and CLIMIE, 1966; the "heterologous sarcoma" of OBER and TOVELL, 1959) contain two or more types of sarcomatous tissues; for example, rhabdomyoblasts and chondroblasts. Some believe these mixed tumors represent a "malignant metaplasia" of modified endometrial stromal cells (ALZNAUER, 1955). It seems just as logical to assume the cells of these mixed sarcomas originate from the so-called Müllerian epithelium, a tissue which undergoes mesenchymal differentiation during embryonal development, leaving its cellular descendants with partial potentialities for further differentiation (see Table 15). Occasionally the metastases from these mixed tumors consist of only one type of sarcomatous tissue. OBER (1959) regards the prognosis for these heterologous sarcomas to be even worse than that for the homologous endometrial stromal sarcoma.

Other rare types of sarcoma that may occur or develop from the mixed forms are *lymphosarcoma* (SCHLAGENHAUFER, 1912; WALTHER, 1934; BLAUSTEIN *et al.*, 1962; BURROWS *et al.*, 1964; FOX and MORE, 1965; WRIGHT, 1973; CHORLTON *et al.*, 1974), which is thought to arise from the lymphoid follicles of the endometrium; *myelogenous* sarcoma (KAPADIA *et al.*, 1978), as a local manifestation of a myelogenous leukemia (chloroma), *plasmocytoma* (ANDERSON, 1949), malignant *hemangioendothelioma* (ULESKO-STROGANOWA, 1925; COHEN *et al.*, 1949) or *angiosarcoma, chondrosarcoma* (GEBHARD, 1903) and *rhabdomyosarcoma* (R. MEYER, 1930; DONKERS *et al.*, 1972). These tumors are readily recognized by their characteristic cell-types which may show various degrees of differentiation and consequently, pleomorphism; they are all extremely rare. The classification of angiosarcoma into endotheliomas, peritheliomas and so forth seems questionable since so few of these tumors have been described.

Leiomyosarcomas arising in the myometrium may infiltrate the endometrium secondarily. These tumors are densely cellular and characteristically composed of atypical muscle cells in various stages of differentiation. Among almost fully-developed smooth muscle cells one finds shorter spindle cells with few myofibrils and distinctly pleomorphic nuclei. R. MEYER (1930) named such a tumor "sarcoma myocellulare". Ultrastructurally, the cells of these tumors are either poorly differentiated and elongated with numerous polyribosomes and meager Golgi bodies, or are myoblastic with typical myofilaments, or fibroblastic, rich in rough endoplasmic reticulum (BÖCKER and STEGNER, 1975). The nuclei are generally large and hyperchromatic, mitoses abound. Since their number serves as an important criterion for evaluating the invasive potential of the tumor, several portions of tumor should be examined histologically. Those parts with the most mitoses then are used for trying to evaluate the biological behavior of

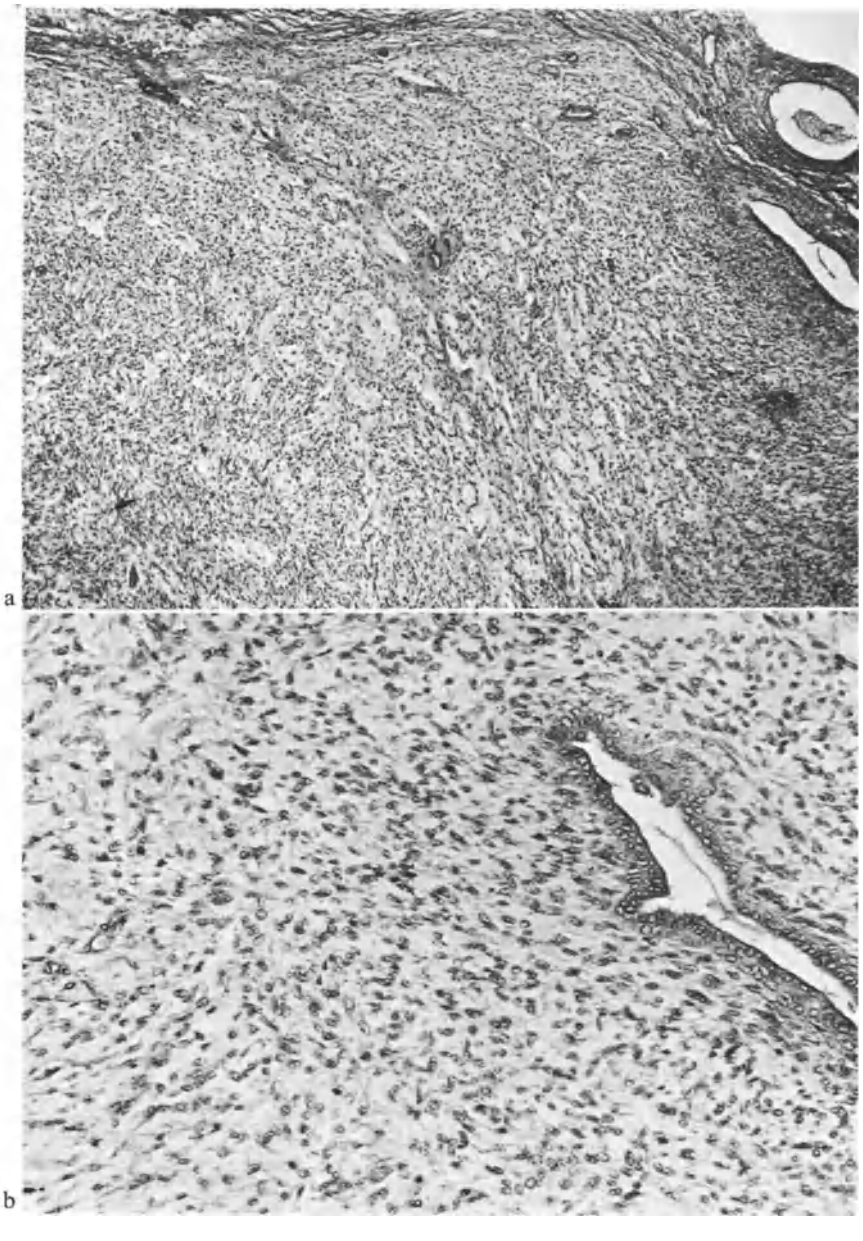


Fig. 98a–d. Homologous endometrial stromal sarcoma infiltrating the myometrium. (a) Low magnification. (b) Higher magnification. (c) and (d) Polypoid surface of an endometrial stromal sarcoma. Curettings may contain only such small polypoid portions of the tumor. At low magnification (c) it may be mistaken for an edematous polyp. At high magnification (d) the sarcomatous character of the abnormal stromal cells can readily be recognized

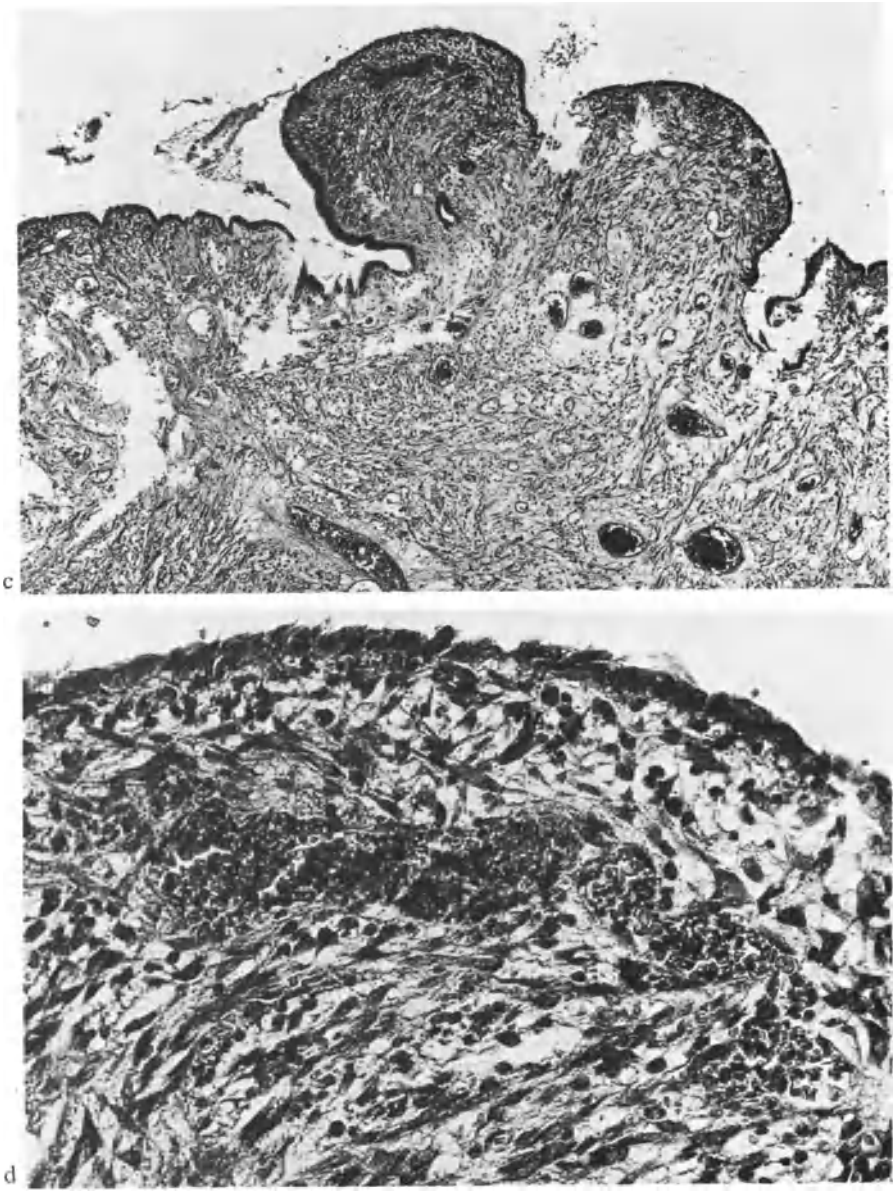


Fig. 98c and d. Legend see opposite page

the tumor. Besides the pure homogeneous leiomyosarcomas, *fibroleiomyosarcomas* may arise with fibroblastic cells predominating (LAFFARGUE *et al.*, 1966). The development of a leiomyosarcoma of the endometrium directly by transformation of stromal cells, as postulated by BIRD and WILLIS (1965), is certainly an exception if it occurs at all. The opposite, the development of a *stromal sarcoma* of the myometrium from a stromal endometriosis ("Endometrioid sarco-

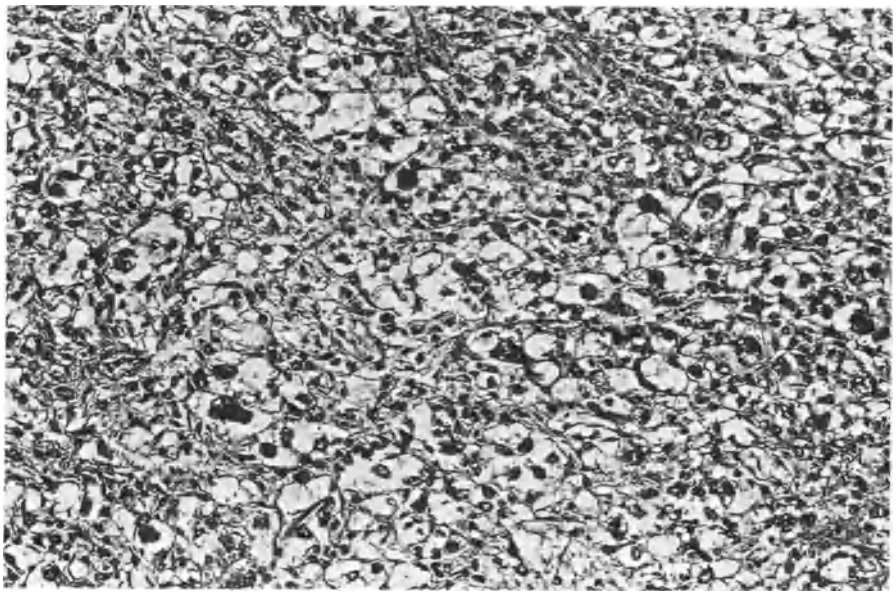


Fig. 99. Polymorphic endometrial stromal sarcoma with giant cells

ma": JENSEN *et al.,* 1966) does occur. Clinically, the tumor is thought to be less malignant than the endometrial sarcoma (SAKSELA *et al.,* 1974; DALLENBACH-HELLWEG, 1980). It may prove exceedingly difficult to differentiate a stromal endometriosis *(endolymphatic stromatosis)* from a stromal sarcoma of the endometrium or myometrium (RUPPERT, 1949; HUNTER *et al.,* 1956; LAFFARGUE *et al.,* 1966; GOLDMAN and GANS, 1967). It is often possible, however, by using the low number of mitoses as criterion (YOONESS and HART, 1977). TAVASSOLI and NORRIS (1980) describe rare focal, nodular stromatoses of the endometrium. Although clinically benign, they cytologically resemble low-grade sarcomas, from which they can be distinguished only by their clearly demarcated margins and their expansile (non-invasive) mode of growth.

Occasionally during treatment of a glandular-cystic hyperplasia with progesterone the endometrial stroma undergoes a *pseudosarcomatous proliferation,* its cells developing large, pleomorphic and hyperchromatic nuclei and its glands atrophying (DOCKERTY *et al.*, 1959; CRUZ-AQUINO *et al.*, 1967). Such endometrial changes should not be mistaken for an endometrial stromal sarcoma. They can be distinguished from that tumor by their lack of mitoses. In rare instances, however, an endometrial sarcoma may develop following treatment with some of the synthetic gestagens (cf. p. 236). On the other hand, progesterone therapy may induce regression of a stromal sarcoma and its pulmonary metastases (PELLILLO, 1968).

d) Malignant Mixed Mesodermal Tumors

In addition to the malignant mixed mesenchymal tumors arising from the endometrial stroma or from Müllerian epithelium with its inherent mesenchymal

Table 15. Malignant mixed tumors, sarcomas and carcinomas of the uterine mucosa

Cell of origin	Designation	Interpretation
Müllerian epithelium (pluripotent)	1. Malignant mixed Müllerian tumor	1. Heterologous combination-tumor (R. MEYER, 1930)
	2. Sarcoma botryoides	2. Juvenile form of the heterologous combination-tumor (STERNBERG *et al.*, 1954)
	3. Carcinosarcoma	3. Homologous combination-tumor (R. MEYER, 1930)
Müllerian epithelium with mesenchymal differentiation (partial pluripotent)	Malignant mixed mesenchymal tumors (chondro-, osteo-, rhabdomyosarcoma etc.)	Pure heterologous tumor (OBER and TOVELL, 1959)
Müllerian epithelium with epithelial differentiation (partial pluripotent)	Malignant mixed epithelial tumors (clear-cell, socalled hypernephroid adenocarcinomas, mucoepidermoid carcinomas)	Pure heterologous tumor
Epithelial cells and stroma cells of the endometrium (fixed potentialities)	Carcinosarcoma	Composition-tumor (R. MEYER, 1930)
Epithelial cells and stromal cells of the endometrium separate (fixed potentialities)	Carcinoma and sarcoma	Collision-tumor (R. MEYER, 1930)
Stromal cells of the endometrium (fixed potentialities)	Endometrial stromal sarcoma	Pure homologous tumor (OBER and TOVELL, 1959)
Epithelial cells of the endometrium (fixed potentialities)	Mature and immature adenocarcinoma, adenoacanthoma	Pure homologous tumor

↓ Loss of potentialities

potentialities, other malignant tumors may develop that have epithelial as well as mesenchymal components. Consequently, we call these carcinosarcomas, or malignant mixed mesodermal tumors. They constitute about 60% of all uterine sarcomas (SALAZAR *et al.*, 1978). Under that heading R. MEYER (1930) distinguished between the combination-tumors, the composition-tumors, and the collision-tumors. *Combination-tumors* are those in which both epithelial and stromal cells arise from the same pluripotential stem-cells, as for example, the carcinosarcomas that develop directly from the epithelial-like cells of the Müllerian duct (see Table 15). Since the sarcomatous and carcinomatous components of the *composition-tumors* probably also arise from mesenchymal and epithelial tissues of the endometrium, albeit from differentiated and more mature cells, it would

seem logical to group the composition-tumors with the combination-tumors. The sarcomatous cells of these composition-tumors, as might be expected from their reduced potentialities to differentiate further, are homogeneous. Those of the combination-tumors, however, may vary greatly because of the pluripotentialities of the undifferentiated Müllerian epithelium from which they arise; they may, for example, contain both myxomatous and chondromatous parts (SCHRÖDER and HILLEJAHN, 1920; ROEMER, 1941; MOEGEN, 1951; BERGER and DIETRICH, 1957; TAYLOR, 1958; CARTER and MCDONALD, 1960; HOFFMEISTER and HANSCHKE, 1960, and others). Consequently, these heterologous combination-tumors have recently been renamed "malignant mixed Müllerian tumors" (STERNBERG *et al.*, 1954; JOPP and KRONE, 1962) or as "Mülléroblastome" (MARTIN *et al.*, 1956).

These truly mixed tumors should be differentiated, on the one hand, from the collision-tumors that develop according to R. MEYER from the growing-together of a carcinoma and a sarcoma, each of which originates separately. On the other hand, we should separate the mixed tumors from poorly differentiated adenocarcinomas whose peripheral portions appear sarcomatous (the carcinoma pseudosarcomatodes of E. KAUFMANN) or whose stroma assumes a sarcoma-like appearance, a change thought to be caused by abnormal metabolic processes of the tumor cells (MARIANI *et al.*, 1957).

Collision-tumors may develop in various ways: 1) A malignant change of the epithelial cells and stromal cells may be induced at the same time by the same stimulus (JOPP, 1965); 2) the carcinoma may provoke an abnormal hyperplasia of the stroma which in turn leads to development of the sarcoma (HARVEY and HAMILTON, 1935; HINZ, 1952); 3) the sarcoma may stimulate the development of the carcinoma (SEHRT, 1905). Sarcomatous polyps that are invaded by adenocarcinomatous cells either at the surface or at the base (ALBRECHT, 1928) also belong to the collision-tumors. Both components, however, may remain separated (BREITER, 1938).

When the growth of a tumor is well-advanced, it may be very difficult if not impossible to distinguish a collision-tumor from a true combination-tumor or a composition-tumor. If a mixed tumor is suspected, it is important to take samples of tissue from different parts to insure that the histological study is complete. Such thorough studies may reveal that a tumor presumed to be a pure carcinoma or sarcoma is instead a mixed tumor. Such a disclosure is important for the therapy and prognosis. Recent studies indicate that mixed tumors are more common than previously assumed. Every large polyp with a smooth surface might be a mixed tumor and should be studied histologically (TAYLOR, 1958).

The **carcinosarcomas** of the endometrium, comprising the homologous combination-tumors and the composition-tumors, account for about 1.2 per cent of the corpus carcinomas (BRÄUNIG and LOHE, 1968). The average age of the patients, as calculated from larger statistics, is 62 years (NORRIS *et al.*, 1966) or 61.3 years (BARTSICH *et al.*, 1967). The youngest reported with such a tumor was a girl 14 $^1/_2$ years old (LANCET and LIBAN, 1970). About 50 per cent are nullipara. A *previous X-ray irradiation* (2000–8000 R from one to eighteen years before, with an average of 16.4 years) to the small pelvis seems to be important etiologically in the development of the tumor. BARTSICH *et al.* (1967) obtained

a history of such therapy in 37 per cent of their patients with carcinosarcoma; BOUTSELIS and ULLERY (1962) found it in 17 per cent; NORRIS and TAYLOR (1965, 1966) reported that 12 per cent of all their patients with a uterine sarcoma and 13 per cent of their patients with carcinosarcomas had received previous X-ray therapy. SPEERT and PEIGHTAL (1949), HILL and MILLER (1951), SYMMONDS and DOCKERTY (1955), VELLIOS *et al.* (1963), O'CONNOR (1964), PILLERON and DURAND (1968), THOMAS *et al.* (1969) and many others also disclosed that a high percentage of their patients with carcinosarcoma had previously been given X-ray therapy. Some hold that prior therapy with estrogen may be of etiological importance (KARPAS and SPEER, 1957).

Grossly, the carcinosarcomas almost always bulge into the uterine cavity as soft, pedunculated polyps; they may even protrude from the outer cervical os. On section the tumors appear gray-yellow. They invade the myometrium and lymphatic channels early, soon reach the structures of the small pelvis (adnexae, bladder, and rectum), then spread throughout the peritoneum, into the vagina, and metastasize to the paraaortic, paraesophageal and paratracheal lymph nodes, and hence to the liver and lungs.

Most investigators report that the *prognosis* is very poor (OBER, 1959). The average length of survival after the first clinical symptoms appear varies from six to twelve months (HILL and MILLER, 1951; STERNBERG *et al.,* 1954; TAYLOR, 1958, 1972; BRÄUNIG and LOHE, 1968). HALL and NELMS (1953) as well as BARTSICH *et al.* (1967) never saw a patient survive five years and 77 per cent of the patients lived less than two years. In the series reported by NORRIS and TAYLOR (1966), 70 per cent of the patients died between one month and five years after therapy was started. WILLIAMSON and CHRISTOPHERSON (1972) observed a five year survival-rate of only 20.5 per cent. Women with homologous mixed tumors, however, survive longer than the women with heterologous mixed Müllerian tumors (OBER, 1959; KRUPP *et al.*, 1961). Of these latter tumors, those showing chondroblastic differentiation have a slightly better prognosis than those containing rhabdomyoblasts (NORRIS *et al.*, 1966; BÖCKER and STEGNER, 1974). Thus, it is important to differentiate histologically between these two types. The extent of tumor growth at the time of operation is especially important for evaluating the prognosis (CHUANG *et al.*, 1970). In the series of MORTEL *et al.* (1974), the 5-year survival was 60 per cent when the tumor was limited just to the uterus, compared with 32 per cent for the overall series. The age of the patient is also important: premenopausal patients have a slightly better prognosis than those postmenopausal.

Histologically, the homologous carcinosarcomas (homologous combination and composition tumors of R. MEYER) consist of tubules or cords of carcinoma cells usually in various stages of maturity intimately surrounded by the sarcomatous stroma. The carcinomatous gland-like structures may exist either as small acini or as large follicles. Their lining epithelial cells, which often contain PAS positive substances, may form papillae. Occasionally foci of squamous metaplasia are seen with well-developed pearls of keratinized cells. In short, the carcinomatous component may reveal all the variations of an adenocarcinoma. The sarcomatous components have potentialities that are fixed and the sarcomatous cells generally are all spindle-shaped like those of endometrial stromal sarcomas. Occasionally, however, they may become pleomorphic and large, just as those of endometrial stromal sarcomas may (Fig. 100c).

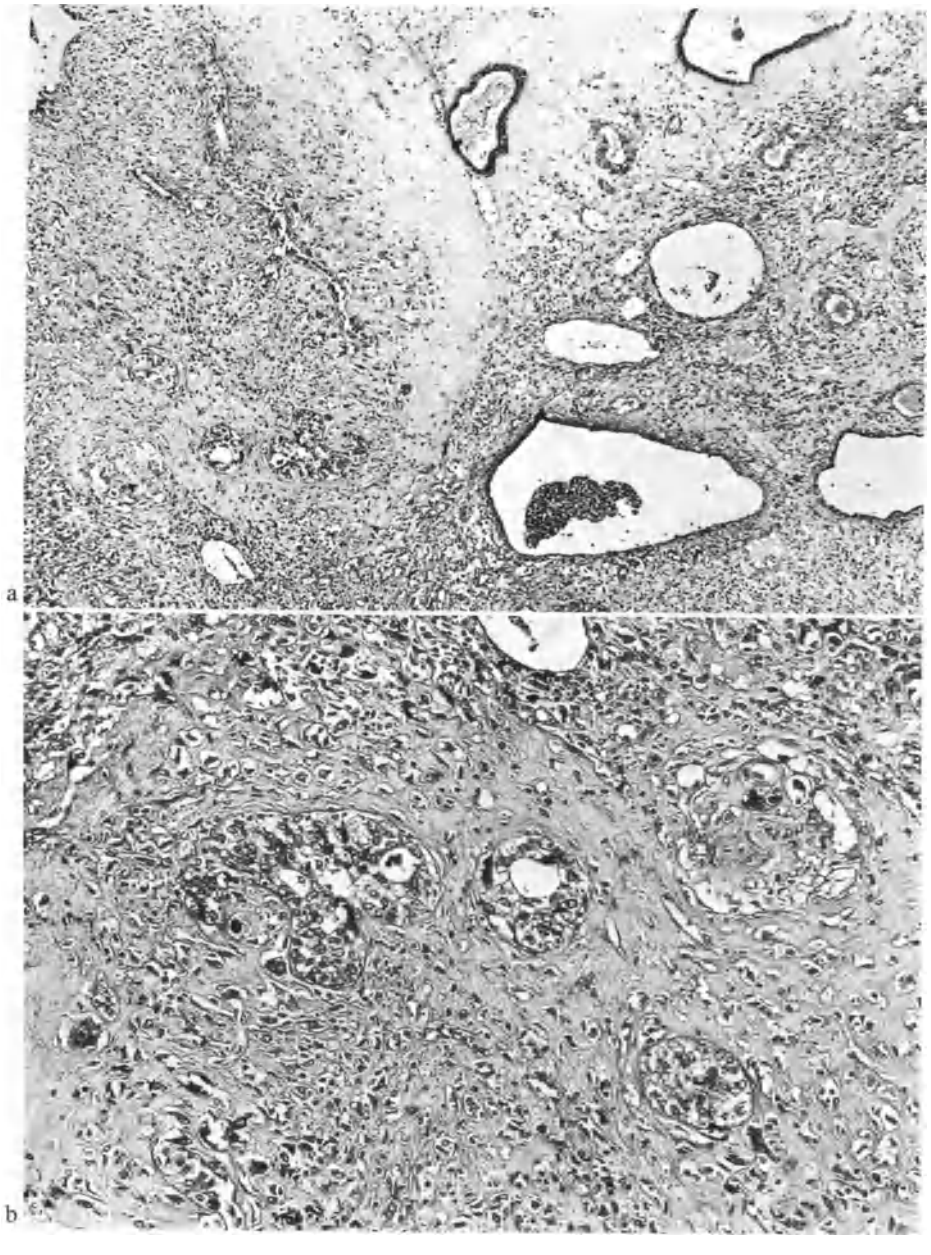


Fig. 100a–c. Malignant mixed Müllerian tumor with heterologous sarcomatous and carcinomatous components. (a) Low magnification. (b) Higher magnification. (c) Carcinosarcoma, also derived from pluripotent Müllerian epithelium (cf. Table 15), is a homologous combination-tumor

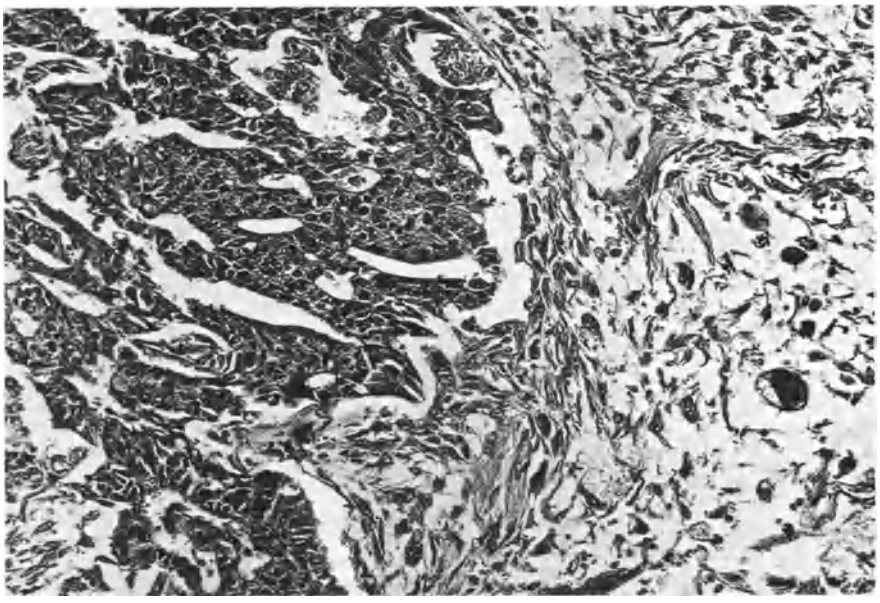


Fig. 100c

On the other hand, in the **malignant mixed Müllerian tumors** (the heterologous combination-tumors) the sarcomatous components may be extremely pleomorphic. Next to poorly differentiated mesenchymal cells one often finds bizarre forms of chondrocytes and osteoblasts, of muscle cells with cross-striations, of fat cells (MORTEL *et al.*, 1970) and of ganglion cells (RUFFOLO *et al.*, 1969); myxomatous transformation also occurs (Fig. 100). Electron-microscopically, all developmental stages from primitive mesenchymal cells to differentiating rhabdomyoblasts and chondroblasts can be identified, providing further evidence for the hypothesis that these tumors arise from pluripotential Müllerian epithelium (SILVERBERG, 1971; BORAM *et al.*, 1972; BÖCKER and STEGNER, 1975). The carcinomatous portions of these heterologous mixed tumors differentiate along all lines possible for the Müllerian epithelium. They may form not only papillary structures but also mucus-secreting endometrial glands, or may contain fallopian-tube-epithelium or psammoma bodies (KRUPP *et al.*, 1961; LAUCHLAN, 1968). Their capacity to differentiate is limited, however, to only those forms that normally develop from the Müllerian epithelium. These tumors differ therefore from the teratomas (STERNBERG *et al.*, 1954). Occasionally mixed Müllerian tumors may arise within a polyp. If still limited to it when first detected the prognosis may be favorable (BARWICK and LIVOLSI, 1979). Those arising from a papillary cystadenofibroma retain their characteristic histological structure (cf. p. 160).

The metastases of these mixed Müllerian tumors may consist of both carcinomatous and sarcomatous elements, or of only one of these components; the purely carcinomatous metastases are more common than those of only sarcomatous elements (HERTIG and GORE, 1960; BARTSICH *et al.*, 1967).

The tumors arising after previous radiotherapy are generally heterologous and develop in the younger women (VARELA-DURAN *et al.,* 1980).

The *sarcoma botryoides* of children, which arises from the cervical mucosa, is analogous to the malignant mixed Müllerian tumor that develops from the adult endometrium. As STERNBERG *et al.* (1954) explained, the reason these two tumors correspond is that the endocervical stroma of children is like adult endometrium. Later, with sexual maturity the endocervical stroma changes. Since the sarcoma botryoides resembles both grossly and microscopically the malignant mixed Müllerian tumors and differs from them only in its site of origin, it may be grouped with them. It grows from the cervix in polypoid, grape-like clusters, and may be composed of sarcomatous parts of diverse character containing cords and gland-like structures of carcinomatous cells. The prognosis of the sarcoma botryoides is the same as that of the malignant mixed Müllerian tumors. When it arises in the cervix, it often invades the endometrium secondarily. It may also arise in the vagina in children, for the vaginal stroma at such an age resembles that of the endometrium.

Based on ten cases, CLEMENT and SCULLY (1974) have recently described a new type of Müllerian mixed tumor of the endometrium. They named the tumor a *"Müllerian adenosarcoma"* to emphasize that its adenomatous component is histologically and biologically benign and its stromal component is definitely sarcomatous. That may also be heterologous, with rhabdomyoblasts and chondroblasts mixed in among the stromal cells, but all are of low grade malignancy (ROTH *et al.,* 1976), rendering thereby a more favorable prognosis. VALDEZ (1979) recently published another example of the adenosarcoma. Its characteristics differentiate it from the homologous carcinosarcoma and the heterologous types of Müllerian mixed tumors.

e) Metastatic Tumors

The carcinomas that metastasize to the endometrium most commonly originate in either the cervix, or ovaries, or fallopian tubes. They usually reach the endometrium by way of lymphatic channels; their spread by way of the fallopian tube (for ovarian carcinomas) or blood vessels is rare.

MITANI *et al.* (1964) found the endometrium to be involved in 25 per cent of the *portio and cervix carcinomas* operated on, even in eight of fifty-seven patients with stage I carcinoma. Even an endocervical carcinoma in situ may spread to the endometrium and involve endometrial glands (SALM, 1969; KANBOUR and STOCK, 1978; WILKINSON *et al.,* 1980). It is important to recognize when the endometrium is invaded since that involvement makes the survival rate worse (PEREZ *et al.,* 1975). The prognosis was somewhat better when spread of the tumor was limited to the endometrium than when it also involved the myometrium. Since in most patients the cervical tumor is evident clinically, no diagnostic problems arise in recognizing the metastatic carcinoma when separate curettings are taken from cervix and endometrium (Fig. 101).

When either the papillary adenocarcinoma of the ovary, the most common *ovarian carcinoma* (NEUMANN, 1927), or the rare *adenocarcinoma of the fallopian tube* (OLESEN and ALBECK, 1949) metastasizes to the endometrium, the site of

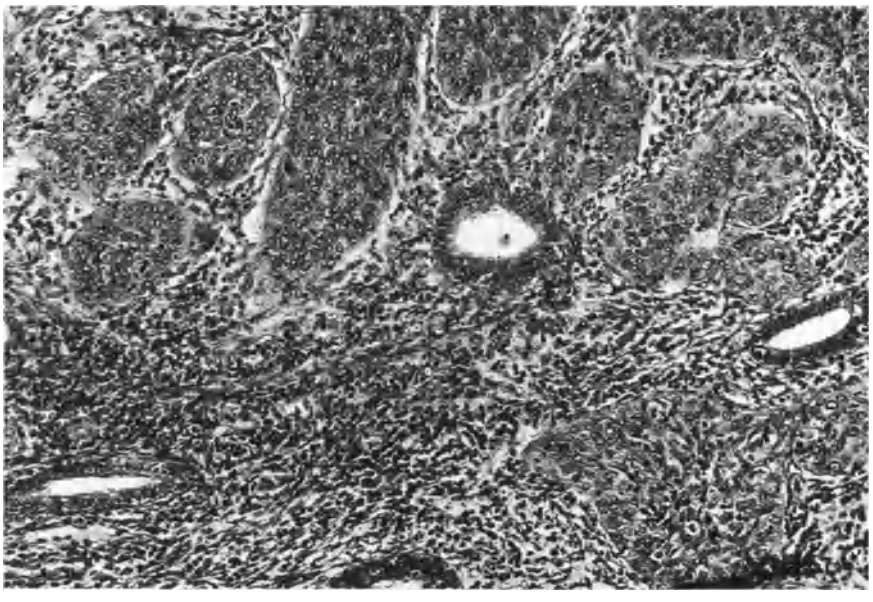


Fig. 101. Extension of an epidermoid carcinoma of the cervix into the endometrium

origin of the primary tumor may not always be obvious. In curettings these tumors are usually misdiagnosed as primary endometrial carcinomas because they histologically resemble one another so closely. Such cases become clarified only after the surgical specimen is examined. On occasions the tumor in the curettings reveals a special type of differentiation that points to the site of origin of the tumor (for example, psammoma bodies). When these bodies are found in a papillary adenocarcinoma, they most probably indicate that the primary tumor has arisen in the ovary. If they are seen in an adenocarcinoma with small acini, then a primary carcinoma of the rectum should be considered. The extremely rare primary psammocarcinomas of the uterus (see p. 177) are solid, and usually free of glandular structures.

In the differential diagnosis several questions should be raised: is the tumor really a metastasis from a carcinoma of the adnexa, or is it a second primary tumor, or does the adnexal tumor represent a metastasis from a primary endometrial carcinoma? In 79 per cent of the cases these questions can be answered (KOTTMEIER, 1953). If, however, the tumors at both the endometrial and adnexal sites appear histologically similar and have reached about the same size, then these questions may prove difficult to settle (KAYSER, 1959; WOODRUFF and JULIAN, 1969). In some cases when a radical hysterectomy is performed, it may be possible to draw conclusions from the anatomy of the tumor spread. When the mucosa of an organ (here the fallopian tube or uterus) is the primary seat of a tumor, or an ovarian cystadenoma undergoes malignant transformation, the changes are so characteristic there is no problem in saying where the tumor arose. Histological criteria, on the other hand, may not prove as reliable. For example, the endometrioid carcinoma of the ovary microscopically looks just like an endometrial carcinoma. That should not surprise us, since both the ovary

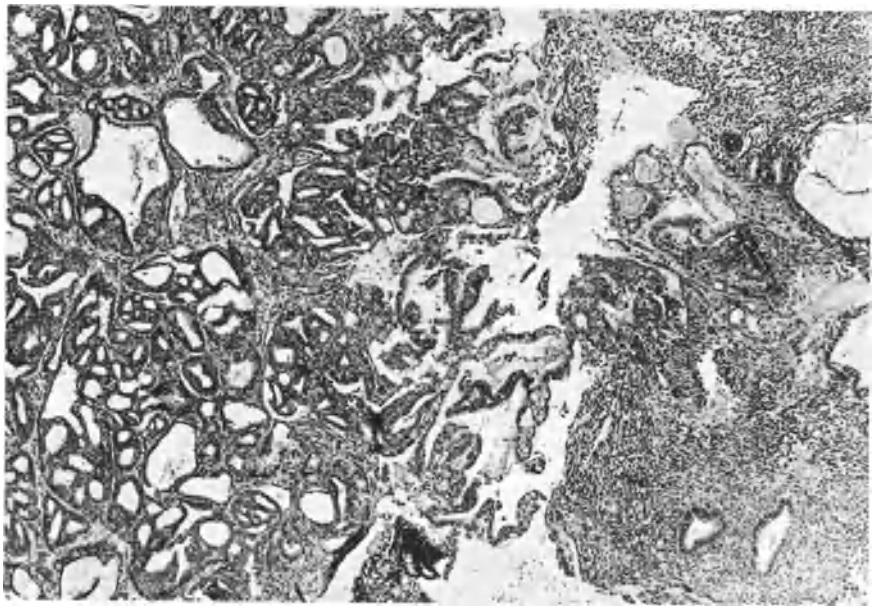


Fig. 102. Metastasis of an adenocarcinoma of the breast (at the left) to the endometrium. Such a metastasis can usually be distinguished from a primary endometrial adenocarcinoma by its discrete and sharp localization, and by its type of glandular structure, characteristic of the breast but not of the endometrium

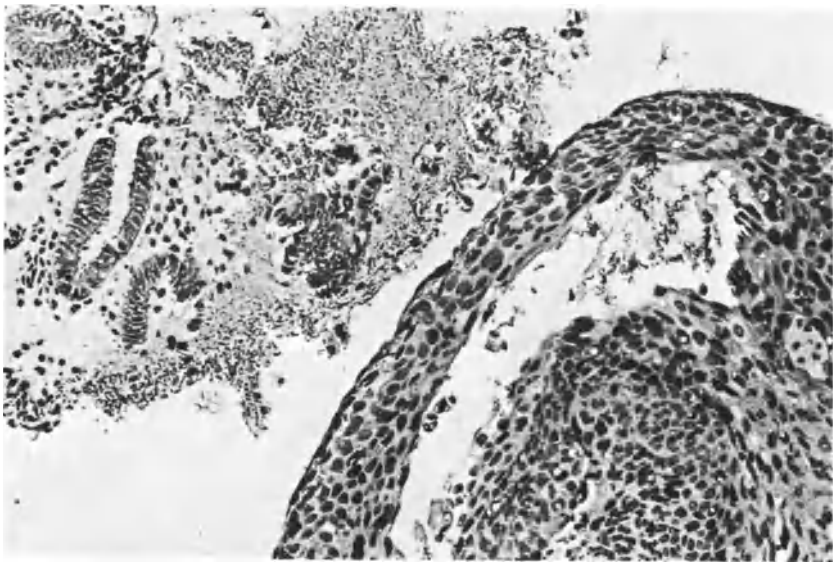


Fig. 103. Sheets of cells in curettings either from a carcinoma in situ or from marginal portions of a carcinoma

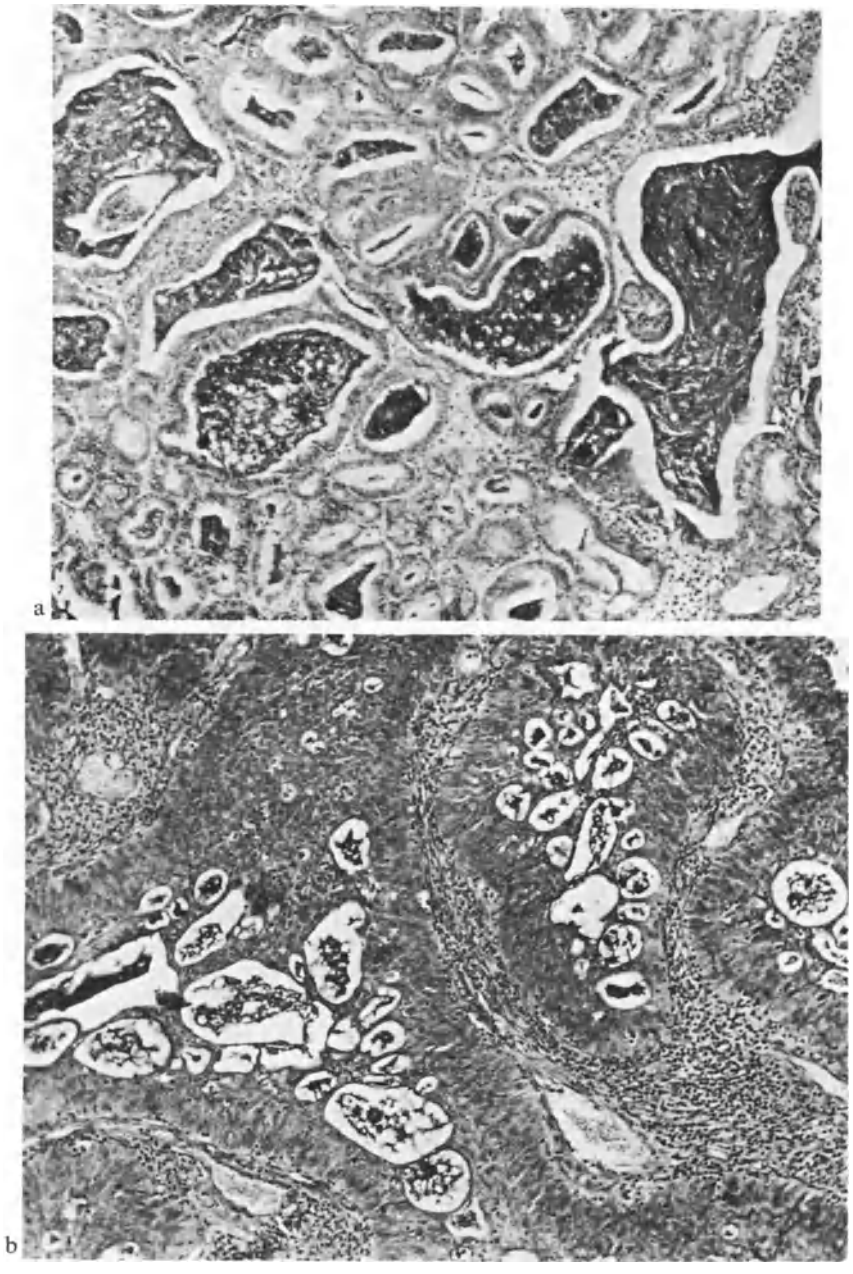


Fig. 104a and b. Mucin-secreting adenocarcinoma of the endocervical mucosa. (a) Mature. (b) Immature

and endometrium originate from the Müllerian duct. About 4 per cent of ovarian carcinomas metastasize to the endometrium and about 4 per cent of endometrial carcinomas metastasize to the ovaries (HERTIG and GORE, 1960).

In contrast, metastases to the endometrium from distant primary carcinomas are rare, having been reported only as single observations. Metastatic carcinomas of the endometrium after resection of a *breast carcinoma* (ESCH, 1929; SZEGVARY *et al.*, 1963; KLAER and HOLM-JENSEN, 1972) can be recognized and safely diagnosed as such when the endometrial tumor retains the typical solid, microalveolar or scirrhous qualities of the primary breast tumor (see Fig. 102). Difficulties in diagnosing metastases arise when the endometrial tumor is a well-differentiated adenocarcinoma. What is more likely in these cases is that after one target-organ for estrogen (breast) is removed, another primary tumor (endometrial carcinoma) arises in a second target organ (endometrium). WEINGOLD and BOLTUCH (1961) found an isolated metastasis from a breast carcinoma in a leiomyoma of the myometrium; the endometrium was not involved.

RATNER and SCHNEIDERMAN (1948) reported on the spread of *renal-cell carcinoma* to the uterus, and OBIDITSCH-MAYER (1951) on uterine metastases from *bile-duct carcinomas*. Metastases from *carcinoma of the stomach*, a very common tumor in Japan, have been observed in the uterus (STEMMERMANN, 1961); three times in the endometrium and five times in the endocervix. POST *et al.* (1966) described the *metastasis of a primary carcinoid of the ileum and appendix* to the uterus. Other investigators have observed single cases in which an *adenocarcinoma of the bronchus* metastasized to the endometrium.—A *leukemic infiltration* of the endometrium may be expected with a generalized chronic leukemia (MCDONALD and WAUGH, 1939; cf. KAPADIA *et al.*, 1978).

f) Primary Carcinomas of the Cervix (Ectocervix and Endocervix) as Components of Curettings

Since the endometrial curette must pass through the endocervical canal, with a complete curettage one can always expect to find some fragments of endo- and ecto-cervical mucosa in the curettings. If a carcinoma is clinically suspected, it is advisable to scrape the endocervical canal first and collect these curettings separately before scraping the uterine cavity. With such a procedure the tumor can be localized. Even when the curettings are not collected separately, in the majority of cases it is possible to say from the histological studies where the tumor arises. In considering now only the *carcinomas* of the uterus (the sarcomas and carcinosarcomas, which spread throughout the uterus early, have already been discussed) the possible types that may occur are:

Histological type	*Site of origin*
1. Hornifying squamous cell carcinoma	ecto- and endocervix
2. Non-hornifying epidermoid carcinoma	ecto- and endocervix
3. Muco-epidermoid carcinoma	ecto- and endocervix
a) solid-cystic variety	ecto- and endocervix
b) glandular variety	ecto- and endocervix
4. Clear-celled carcinoma	endometrium
5. Mucus-secreting adenocarcinoma	endometrium
6. Adenoacanthoma	endometrium
7. Poorly differentiated adenocarcinoma	endometrium
8. Well-differentiated adenocarcinoma	endometrium

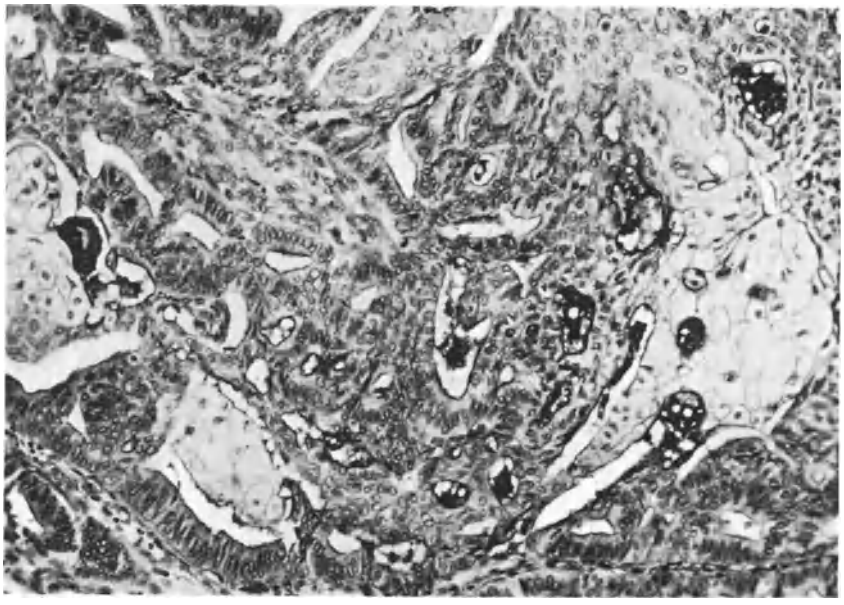


Fig. 105. Mucoepidermoid carcinoma of the endocervical mucosa, glandular type

The less a uterine tumor differentiates, the less it resembles the tissue from which it arises and the greater the difficulty in classifying the tumor or in stating where it arises. Most of the types of tumor that commonly occur, however, can be classified (DALLENBACH-HELLWEG and BRÄHLER, 1960).

Desquamated lamellae of *a hornifying or non-hornifying squamous cell carcinoma* most probably come from the portio, or depending on the extent of tumor-growth and the age of the patient (on displacement of the squamo-columnar junction), they may originate from the endocervical canal. If the curettings contain only single lamellae of atypical epithelial cells (Fig. 103) so that their relation to the stroma cannot be determined, then a carcinoma in situ may also be present. To clarify such cases a conization of the cervix is necessary. It is very rare to find a carcinoma in situ or even an invasive carcinoma arising on the surface of a cervical polyp (FETTIG and SIEVERS, 1966).

The pure *adenocarcinoma* of the cervical mucosa differs from the adenocarcinoma of the endometrium principally in that it produces more mucus and of a different kind (see p. 174), and its epithelial cells usually form single rows without papillae (Fig. 104). The mixed tumors, which characteristically originate from partially potent cells located at the union of squamous epithelium with columnar epithelium, exhibit various degrees of maturation: the *mucoepidermoid carcinoma* differentiates in two directions—in that taken by the portio epithelium, and in that by the endocervical epithelium. Thus, we find this tumor composed of strands of hornifying carcinoma cells admixed with either glandular or solid-cystic formations that produce mucus (Fig. 105). In contrast to the rare clear-cell carcinomas of the endometrium, the *clear-cell carcinomas* of the endocervix fail to produce glandular structures (Fig. 106); because these tumors are poorly

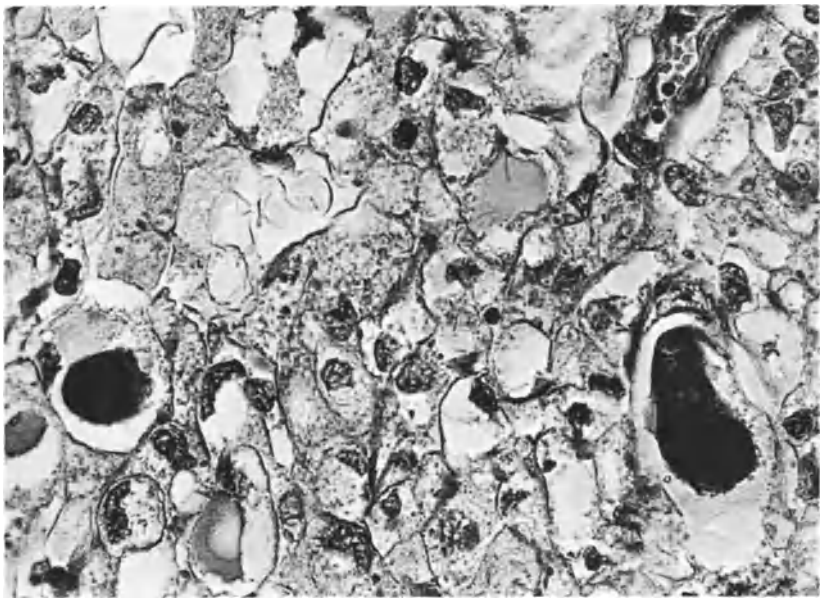


Fig. 106. Clear-cell carcinoma of the cervical mucosa

differentiated it is difficult to classify them. They produce only scanty amounts of mucus or glycogen. Structurally their cells resemble modified precursors of the cervical epithelium.

As to be expected, all types of *intermediary forms* may be found between pure squamous cell carcinomas, pure adenocarcinomas, and the mixed tumors. The beginning transitions may appear as unicellular formations of mucus or keratin in either solid tumors or gland-producing tumors. When we give such transitional forms a name, we should hold to the principal: a potiori fit denominatio, "what predominates determines the name". With that attitude in mind, it is possible from most curettings to state with fair accuracy where the tumor most likely arises. A definitive answer, however, can be obtained only from the resected uterus if the tumor has not already destroyed anatomical landmarks.

5. Iatrogenic Changes of the Endometrium

a) After Hormonal Therapy

As soon as an understanding of the menstrual cycle was achieved and it became obvious histologically that the ovarian hormones induced cyclic changes in the endometrium, attempts were made to treat patients who suffered hypophyseal dysfunction or deficient ovarian function by giving them ovarian hormones to compensate for their endocrine deficiencies. It soon became apparent, however, that every patient reacted uniquely, that the correct time, duration, dosage, and combination of hormonal therapy depended mainly on the state of the

patient's endocrine system. When the doses of ovarian hormones exceeded physiological amounts, they caused characteristic histological changes in the endometrium never seen under normal circumstances. In addition, the effects of many of the synthetic estrogens and gestagens differ from their natural counterparts, depending on their chemical structure and biological potency.

α) Estrogens. The hormones grouped together and referred to as estrogens, although in their action similar, are chemically heterogeneous. The group includes various naturally occurring hormones, some of which are unique to certain species of animals, as well as synthetic steroids and non-steroidal agents. Of the estrogens secreted in the human, estradiol possesses the greatest affinity for the estrogen receptors. Because of their therapeutic advantages, orally active derivatives of estradiol (17α-ethinyl-estradiol, or its methyl ether, mestranol) are especially useful, for example as oral contraceptive agents. Other important prototypes of estrogens are quinestrol ("Estrovis") and the conjugated estrogens ("Premarin", "Presomen", and "Oestrofeminal"), all of which have been used to treat estrogen deficiency. Because stilbestrol has been found to have carcinogenic side-effects, it is not used anymore.

The estrogen potencies of these substances also vary even when they are administered by optimal routes (Table 16). The potencies, however, may be inversely proportional to the affinities the hormones have for estrogen receptors, since the substances are often slowly converted into estradiol, whereby their blood levels are maintained for long periods. Consequently, the estrogen potency of mestranol exceeds that of natural estradiol; and ethinyl-estradiol is one and a half times more active than mestranol when tested for its stimulation of stromal growth, and twice as active when tested for its stimulation of glandular growth (Delforge and Ferin, 1970). These differences can not be detected histometrically (Brosens and Pijnenborg, 1976). Individual fluctuations in the responsiveness to hormones should be taken into account (Hempel *et al.*, 1977). In contrast, estriol (for example, "Ovestin"), which is seldom used clinically, has only one-tenth the potency of either ethinyl-estradiol or stilbestrol (Haskins *et al.*, 1968).

Although the estrogens do show fine distinctions in their effects that are of clinical importance, most of these hormones are extremely potent, even in tiny doses, since the target cells they stimulate are exquisitely responsive to low concentrations and promptly react by characteristic changes. On the other hand, prolonged high doses seem to overwhelm the receptors of the target cells and apparently exhaust the cytoplasmic structures that produce them (Nordquist, 1970) so that specific enzyme systems become blocked (Villee, 1961), and the cells become unable to respond to further estrogen. Atrophy ensues. An estrogenic effect also fails to develop when the receptors have been blocked by clomiphene or norethisterone. For example, in monkeys very high doses of estrogen lead to endometrial atrophy (Hartmann *et al.*, 1941), whereas in other animals (rabbits, mice) prolonged treatment with small doses promotes the induction of carcinoma (Allen, 1942; Dunn and Green, 1963; Graham *et al.*, 1980).

The oral or parenteral administration of estradiol alone from the first day of a menstrual cycle prolongs the proliferative phase and suppresses the secretion

Table 16. The potency of various estrogens ranked by the uterine weight test (after BRIGGS and BROTHERTON 1970)

Diethylstilbestrol dipropionate	14.37
Estradiol 17-cypionate	11.09
Estradiol benzoate	10.75
Estradiol dipropionate	10.00
Ethinylestradiol	9.72
Benzestrol	9.28
Diethylstilbestrol	8.76
Estrone	8.59
Estradiol	8.02
Dienestrol	7.73
Promestrol dipropionate	6.83
Diethylstilbestrol dipalmitate	6.60
Sodium estrone sulphate	4.00
Monomestrol	3.26
Hexestrol	2.48
Estriol	2.26
Control	1.00

of gonadotropins by the pituitary, especially FSH. Development of a corpus luteum is inhibited until the estrogen is discontinued. Menstruation consequently is delayed (ZONDEK, 1940). Treatment with estradiol during the secretory phase results in severe stromal edema (EGGER and KINDERMANN, 1974), delay in secretory transformation of glands and stroma, and a disruption of the nucleolar channel-system, an organelle normally found in the glandular cell nuclei of the secretory endometrium (see p. 23; GORDON *et al.*, 1973). If the estrogen is discontinued after prolonged therapy, an estrogen "withdrawal bleeding" ensues; if the estrogen is given over a long period in consistently small doses, a spontaneous "breakthrough bleeding" occurs. Short-term treatment with progesterone prevents these two types of bleeding. The hemorrhage that follows after the progesterone is discontinued ("progesterone withdrawal bleeding") is never as profuse as with the estrogen "withdrawal bleeding", which is due to tissue necrosis without dissociation of fibers. With only one injection of a depot estrogen the proliferation reaches its maximum after three weeks; thereafter the glands and stromal cells begin to degenerate (HEMPEL and BÖHM, 1976). With prolonged administration of small doses of estradiol (20–100 μg daily) the endometrium responds with glandular-cystic hyperplasia (SCHRÖDER, 1954; BLOOMFIELD, 1957; GREENBLATT and ZARATE, 1967; OBER and BRONSTEIN, 1967; ROSENWAKS *et al.*, 1979; and many others; see Fig. 53). Only estriol is less harmful to the endometrium (SJÖSTEDT and STRANDA, 1971). From time to time portions of these hyperplastic endometria may undergo hemorrhagic necrosis and be discharged, but when the estrogen stimulus continues, unopposed by progesterone, they may progress to *precancerous adenomatous hyperplasias* (see p. 113). With the scanning electron microscope the superficial epithelium becomes furry with numerous, long microvilli. Their length is proportional to the potency of the estrogen administered (NATHAN *et al.*, 1978). Droplets of fat appear in stromal cells of the upper layers of the endometrium (BLACK

Table 17. Synthetic gestagens used in oral contraceptives

		Gestagen potency	Transformation Dose (mg/cycle)
Derivatives of 17α-hydroxypro-gesterone	Megestrol acetate	2.0	35– 50
	Chlormadinone acetate	20.0	20– 30
	Medroxyprogesterone acetate	1.0	40– 70
Derivatives of 19-nor-testosterone	Norgestrel	80.0	12
	Norethynodrel	0.4	150–200
	Lynestrenol	2.7	35– 70
	Ethynodiol diacetate	20.0	10– 15
	Norethindrone (Nor-ethisterone)	1.3	100–150
	Norethindrone acetate	2.7	50– 60
	Quingestanol acetate	5.4	

et al., 1941) and foam cells eventually develop, which store estrogen metabolites or related substances (see p. 114). In contrast to the hyperplasias arising in the pre- and post-climacteric periods because of endogenous causes, those developing after many years of estrogen therapy are characterized by special morphological features: they develop multicentrically and even in the adenomatous stage may be circumscribed or polypoid. In the adenomatous regions the appearance of the nuclei and cytoplasm of the epithelial cells varies from gland to gland. Both flattened and nodular formations of metaplastic squamous epithelium are especially common. Consequently, treatment of patients in the climacterium or after the menopause for long periods merely because of annoying symptoms is not without danger. That danger can be minimized or eliminated when small doses of estrogen are combined with small doses of gestagen. If bleeding develops during therapy, it behooves one to find out why by histological studies.

β) Gestagens. The synthetic gestagens clinically used differ both chemically and metabolically from natural progesterone (SUCHOWSKI and BALDRATTI, 1964). Most are derivatives of 17α-hydroxyprogesterone or 19-nor-testosterone (see Table 17). Although their gestagenic potencies vary considerably, most are more potent than natural progesterone. Norgestrel, which in its d-form is the most active gestagen known at present, is eighty times more active than progesterone. Its high potency may be due in part to its selective uptake by the endometrium, for as radioautographic studies have shown (ZALDIVAR and GALLEGOS, 1971), more norgestrel localizes in the endometrium than does progesterone or chlormadinone. Accordingly, in contrast to the effects of natural progesterone, those produced by the synthetic gestagens closely depend on dosage, but what is really important is not so much the amount administered but the potency of the gestagen used. On the other hand, the potency varies depending on the chemical structure of the gestagen. To determine that potency, the demon-

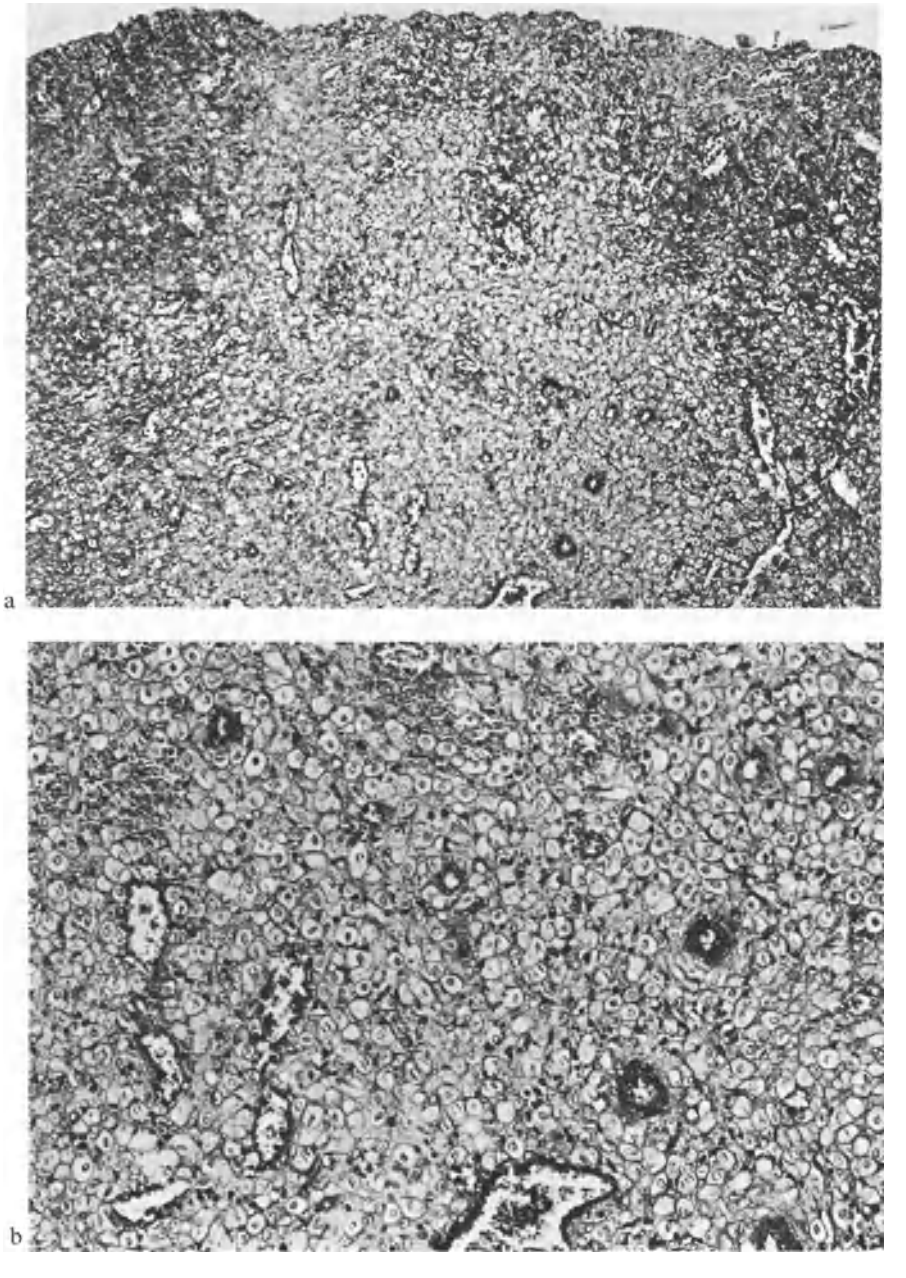


Fig. 107a and b. Stromal cells are transformed into decidual cells ("arrested secretion"). Advanced atrophy of glands and decidual change of stromal cells after many weeks of progestational therapy. (a) Low magnification. (b) Higher magnification

stration of basal vacuoles of glycogen in the glandular cells ("the transformation dose") yields more accurate results than the "delay of menstruation test" (DICKEY and STONE, 1976)

The administration of progesterone alone during the proliferative phase depresses the maturation of Graafian follicles, arrests endometrial proliferation, and postpones or prevents ovulation. If given during the secretory phase, progesterone prolongs the menstrual cycle. When progesterone is discontinued a withdrawal bleeding occurs within a few days; when continued at low doses a breakthrough bleeding develops during therapy. If doses of 5–6 mg chlormadinone are given daily for four weeks or longer, then the secretory change is abolished and the endometrium remains in a state of "*arrested proliferation*" (BAYER, 1965). With treatment beyond six weeks the arrested proliferation gives way to progressive atrophy of the glands and decidualization of the stroma. After three months of continuous therapy, amounting to a total dose of about 500 mg progesterone, a typical appearing decidualized stroma develops with extreme or complete atrophy of the glands: "*arrested secretion*" ("starre Sekretion", WINTER and POTS, 1956; Fig. 107). The same picture can be produced experimentally in castrated monkeys after priming with estrogen (HISAW and HISAW, 1961). Most likely such exogenous progesterone, in the manner of a feedback mechanism, inhibits the secretion of FSH by the pituitary. If treatment is continued it may eventually lead to an irreversible *atrophy* with hyalinization of the stroma (CHARLES, 1964; BAYER, 1965; Fig. 108). Large daily doses induce similar results, but even then the duration of treatment is decisive. The various synthetic gestagens differ both quantitatively and qualitatively in their action.

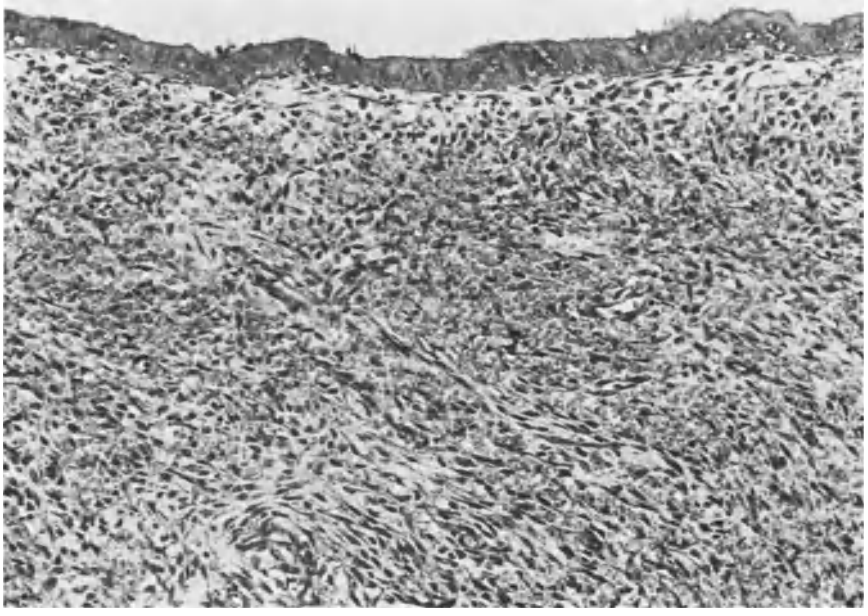


Fig. 108. Atrophy and fibrosis of the endometrium with complete loss of glands after several months of gestagen therapy

The dosage required to produce a transformation of the endometrium varies from preparation to preparation; with progesterone about 200 mg are needed, with the synthetic gestagens considerably less (see Table 17). Moreover, some gestagens may affect mostly the stroma, others primarily the glands. Following therapy with derivatives of 19-nor-testosterone, decidualization is more pronounced and the subsequent atrophy more extreme than with derivatives of progesterone (FRIEDRICH, 1967). Since the glandular epithelial cells are more sensitive to progesterone and react to it earlier than the stromal cells do, the epithelium usually becomes refractory sooner to abnormal stimulation by gestagens, whereas the stroma begins to atrophy only after a prolonged decidualization (DALLENBACH-HELLWEG, 1972).

In using gestagens in the treatment of endometriosis one not only takes advantage of their antiproliferative action (see GUNNING and MOYER, 1967) but also of their effectiveness in producing a protracted delay in menstruation (CARTER *et al.*, 1964). Even after the menopause treatment with gestagens over a long period may lead to the development of a typical decidua, which differs from a decidua of pregnancy only by the atrophy of its glands (Fig. 109; Table 20; p. 283f). Occasionally progesterone therapy is used to inhibit the progression of inoperable endometrial carcinomas and their metastases (see p. 195ff). Gestagens also are of value as substitution therapy, for example, for patients with deficient secretory phases during the last week of the menstrual cycle (GILLIAM, 1955; GLASS *et al.*, 1955; MOSZKOWSKI *et al.*, 1962). Since estrogen is also deficient in some of these patients, they may require treatment with both hormones (ROLAND, 1967). By administering gestagens to a patient with primary amenorrhea (the *progesterone withdrawal test*), it is possible to determine whether the patient

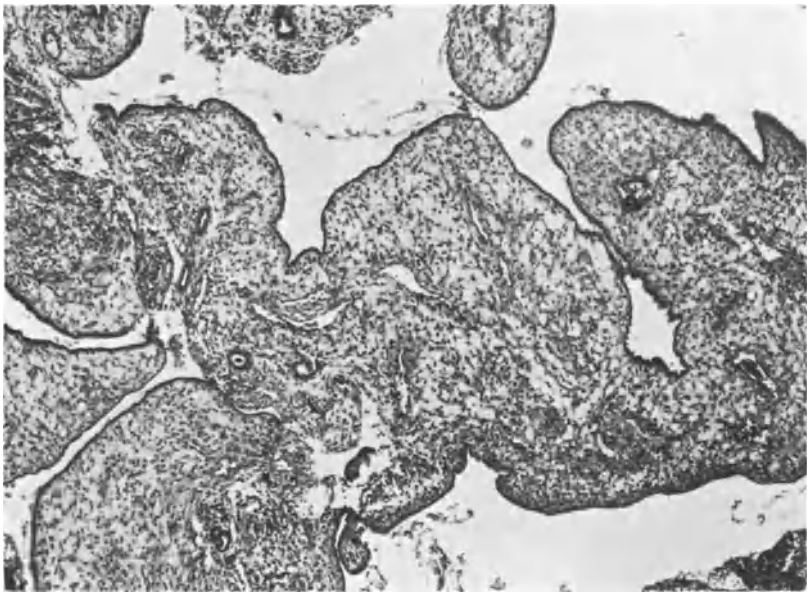
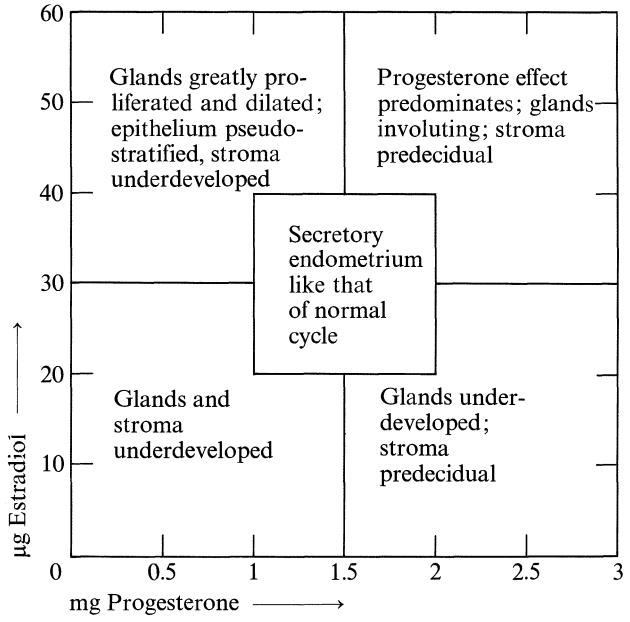


Fig. 109. "Arrested secretion" after 9 months of Orgametril

Table 18. Reaction of the endometrium to the administration of estrogen and progesterone (Modified from GOOD and MOYER, 1968)



produces estrogen or not. The test depends on the fact that the endometrium is unable to respond to progesterone without prior stimulation by estrogen ("estrogen priming"). If the patient does produce estrogen, then a progesterone withdrawal bleeding sets in two to eight days after giving the gestagen. To evaluate the functional state of the endometrium, the *estrogen withdrawal test* may be performed. If the patient fails to bleed after discontinuing estrogen therapy, her amenorrhea is caused by anatomical (for example, aplasia, tuberculosis) or functional (for example, refractory target cells) abnormalities of the endometrium ("uterine amenorrhea").

γ) By administering **both hormones** as they appear in a normal cycle, it proved possible to reproduce a regular menstrual cycle in castrated monkeys (HISAW, 1935) and in castrated women (KAUFMANN, 1933, 1939). What turned out to be important, however, was the relative amounts of the hormones (FERIN, 1954, 1955, 1963; NEVINNY-STICKEL, 1964; GOOD and MOYER, 1968; see Table 18). Depending on the level of endogenous estrogen, the amount of gestagen needed was found to fluctuate considerably (RUDEL *et al.*, 1964). Whereas 30 mg of progesterone may be sufficient to induce a secretory transformation of an artificially induced proliferation phase, about 400 mg are needed to treat a glandular-cystic hyperplasia (GRUNER, 1942). If the dose of estrogen given a castrated woman is too high or the dose of progesterone too low, then the secretory change may either be delayed up to ten days or remain deficient (FERIN, 1963). Because of these fluctuations the normal buildup of the endometrium should be checked histologically and controlled by repeating endometrial biopsies. By

using the long-acting gestagens (e.g., 17-ethinyl-19-nor-testosterone-onanthate) and depot estrogens one application during a cycle is enough to elicit a menstrual-like breakthrough bleeding (DAVIS and WIED, 1957; BOSCHANN and KUR, 1957). These and other synthetic preparations are ideal for treating functional bleeding and secondary amenorrheas (BORGLIN, 1962; DOMINGUEZ *et al.*, 1962; CHARLES *et al.*, 1964). Amenorrheas primarily due to ovarian insufficiency at times require a pretreatment only with estrogen (GOLD *et al.*, 1965; OBER and BRONSTEIN, 1967).

δ) Hormonal therapy in gynecology, even today, is dominated by the **oral contraceptive agents.** Although these medications are occasionally used to correct abnormalities of hormonal regulatory mechanisms (functional bleeding, dysmenorrhea, endometriosis), their main use is for birth control. Based on experimental studies in animals (HABERLANDT, 1921), BICKENBACH and PAULIKOVICS (1944) succeeded in suppressing ovulation in women by administering 20 mg of progesterone daily, just as MISHELL *et al.* did later (1968). The same suppressive effect follows the administration of estrogen alone during the proliferative phase (BOARD and BORLAND, 1964; and many others). Since studies soon showed that prolonged therapy with progesterone alone led to frequent breakthrough bleeding and eventual atrophy of the endometrium, and unopposed estrogen induced endometrial hyperplasia, combinations of both hormones in appropriate dosages were tried. As gestagen, derivatives of 19-nor-testosterone or 17α-hydroprogesterone acetate were used, and are still in use. As estrogen, either 17α-ethinyl-estradiol or its methyl ether, mestranol, was selected because of its potent, prolonged effect. The doses of both hormones initially employed were reduced to the minimal concentrations still affording successful contraception, with the hopes of avoiding side-effects that some patients treated with the first preparations had experienced. One should not forget that it is the potency of the hormones that determines how effective they act, not the dosage (HEINEN, 1971). It is also important to remember that some women metabolize the gestagen components of some of the combination preparations into products having estrogenic and androgenic effects. It has been found that no direct relationships exist between the gestagen activity, that is, the dose of gestagen needed to produce secretory transformation, and the degree of ovulatory suppression (percentage of ovulations inhibited) (TAUSK, 1969). Since 1953, PINCUS and coworkers have extensively studied the use of many different preparations (see PINCUS, 1965). Since then, elsewhere throughout the world, many investigators have introduced and tested countless new combination-preparations of diverse chemical composition in varying dosages, and from the experience gained, have subsequently modified their preparations or developed newer ones. To list all now, as attempted in the first edition of this book, would far exceed the bounds set by its purpose, and the continual, rapid progress in developing new preparations would soon make such a list obsolete. What is important for diagnosing histological changes is not their names but their chemical composition (s. Tables 16 and 17). Most hormonal contraceptives are administered as "combination" preparations, containing both estrogen and progestin, or as "sequential" preparations. The combination agents are taken either as pills for twenty consecutive days each menstrual cycle, usually from the fifth to the twenty-fourth day,

or are given as a single injection or pill that lasts for the same period. Treatment with the sequential agents mimics the natural secretion of hormones by the ovaries, and involves taking a pill of estrogen alone from the fifth to nineteenth days (or fifth to fourteenth days) to suppress ovulation. Thereafter, a pill containing both estrogen and progestin is taken until the twenty-fourth day to produce a secretory change and a menstrual-like breakthrough bleeding (KAISER, 1963; GOLDZIEHER *et al.*, 1964).

Another method is the use of progesterone alone, either orally as a "minipill", to be taken each day, or parenterally as a depot injection. Latest developments are the three sequence preparations, which provide minimal doses of both estrogen and progestin not possible with previous agents. Not only do these latest preparations reduce the overall burden with exogenous hormones, they also interfer less with the secretion of FSH and LH. They have not been used long enough, however, to allow adequate evaluation of the histological changes they might induce.

As the use of all these preparations by healthy women has become more widespread, so have reports about their side-effects bourgeoned to a voluminous literature, covering not only a wide spectrum of changes in many organs and tissues but also disturbances of hematological, endocrinological and neurological function. Since extensive reviews of these innumerable reports are available (for example, KIRCHHOFF and HALLER, 1964; BORELL, 1966; BARBER *et al.*, 1969) there is no need to concern ourselves with them further. What primarily interests the gynecologist and pathologist, however, are the morphological effects of the oral contraceptives on the female reproductive system, and as regards this monograph, their effects on the endometrium.

As we have already noted (see p. 46), the endometrium is our most sensitive indicator for gauging the levels and proportions of the sex hormones in the blood. In healthy women the endometrium responds to exogenous hormonal therapy by very definite histological changes. The mass experiment now being carried out by the users of the antifertility agents has shown beyond all doubt that these endometrial changes take place with a precision that is astounding for a biological system. Consequently, by studying the endometrium and knowing about the hormonal state prior to therapy, it is possible with practice to determine how much and what type of antifertility agent the patient has received. Because most of the oral contraceptives used at present are similar in composition, the endometrium reacts to most in much the same way. Nevertheless, one can detect differences in the effects of some preparations (particularly differences between combination agents and sequential agents) when their dosages and chemical compositions vary (see JACKSON, 1963; ROLAND *et al.*, 1964, 1966; MEARS, 1965; YANEVA *et al.*, 1965; MORF and MÜLLER, 1966; OBER, 1966; RUDEL *et al.*, 1966). One may also perceive distinctive variations that depend upon the patient's state of hormonal equilibrium, and these may vary within physiologic limits between "predominately estrogen" to "predominately gestagen" (TENHAEFF, 1971). Further variations in response among patients may occasionally be seen even when the same preparation is used to treat functional disturbances, since the response depends on the differences in endocrine dysfunction from patient to patient existing prior to treatment.

With almost all **combination preparations** the proliferative phase of the first few cycles is characteristically shortened, consequently the glands and stroma fail to develop completely. Equally characteristic is the premature appearance of persistently deficient secretory changes in the glands and stroma, with the glands remaining uncoiled. These abnormal changes can be readily explained: to reach its peak of proliferation and full development a normal endometrium needs fourteen days of continuous stimulation by estrogen. By using a combination antifertility pill from the fifth day of the cycle on, that estrogen stimulation is prematurely interrupted by the gestagen component, inducing an early arrest of both growth and differentiation of the glandular epithelium at its incompletely developed stage. Continued therapy prevents further development and the epithelium remains immature. Another distinctive feature of the artificially arrested cycle is the remarkable intermingling of glands and stroma in very different stages of maturity, none of which correspond to the true day of the cycle. As a result, the surface of the endometrium becomes uneven, eventually growing rough through knobby outgrowths and polypoid excrescences (Fig. 110). This colorful picture resembles in part that of the deficient secretory phase, which in its hormone-levels also shows certain similarities to the artificially inhibited levels (Fig. 111).

In general, the following changes will be observed to occur *during the first cycles of therapy*. The *endometrial glands* will be unevenly distributed and vary greatly in their development, the degree of variation depending on how long treatment has lasted. Some glands will be distinctly atrophic and narrow; others will be enlarged and at times even cystically dilated, lined usually by small,

Fig. 110. After six months of Anovlar the endometrial surface is nodular, stromal edema is spotty, and the glands are variously developed: Abortive secretion

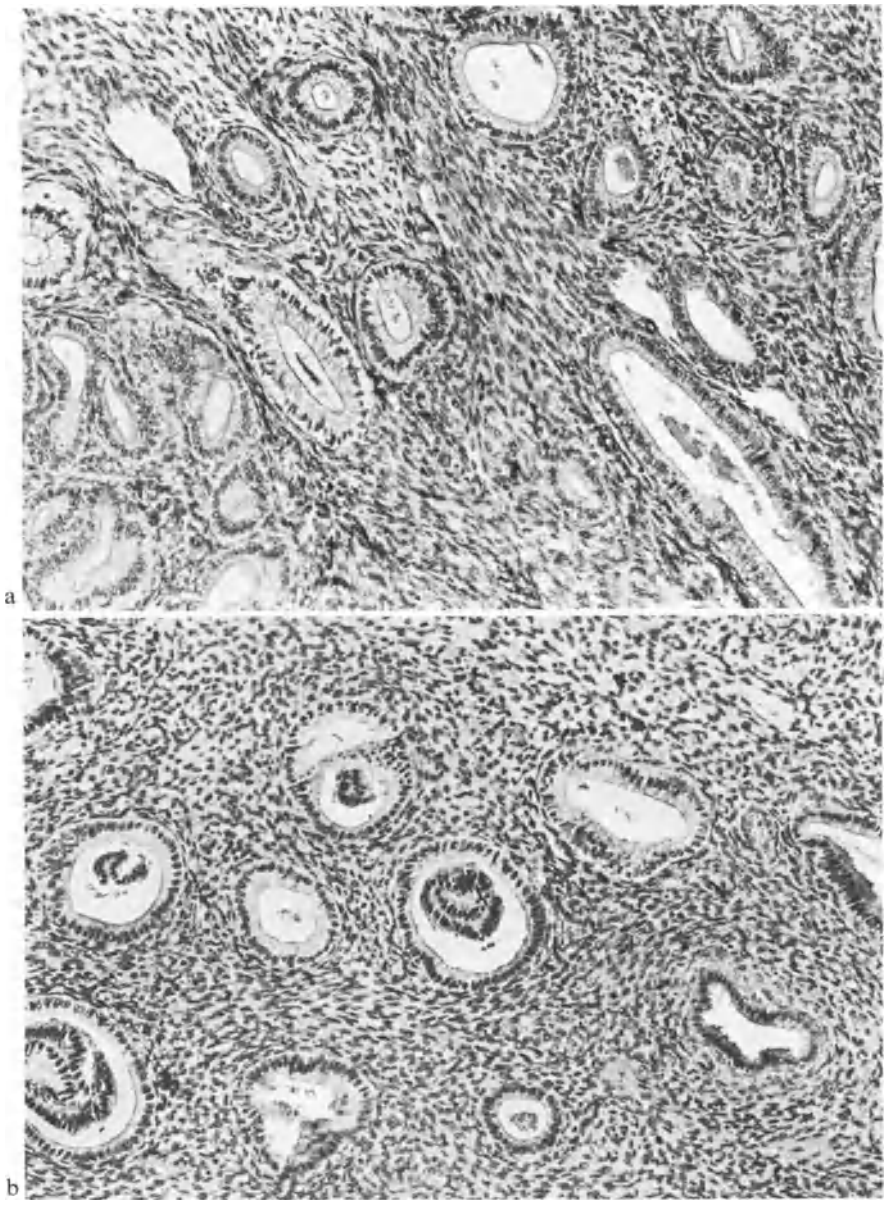


Fig. 111a and b. A prematurely deficient secretory phase. The glands are in various stages of abortive secretion. The stromal cells are spindly. (a) After six months of Anovlar. (b) After six months of Ovulen

low cuboidal epithelial cells, rarely by proliferated, tall columnar cells (Fig. 111 b, 112). Near these glands one will often encounter other glands that are moderately dilated, composed of low epithelial cells with scanty cytoplasm and small, rounded nuclei. Occasionally small or larger vacuoles of glycogen may be found near

the nuclei, which then are located at random. The quantity of glycogen formed will vary, depending on the dosage and composition of the gestagen component of the agent used. After derivatives of progesterone there is more glycogen than after nortestosterone (SIEGEL and HEINEN, 1965). In contrast, glycogen in the lumen is virtually always lacking because its secretion from the cells is inhibited; the apical margin of the cell is always smooth and sharply defined. Acid mucopolysaccharides appear only after derivatives of progesterone, and then merely in small amounts. In the first half of the cycle mitoses are rare. The glandular nuclei contain small nucleoli which electron-microscopically appear rarefied and reveal no nuclear channel-system in the second half of the cycle (CLYMAN, 1963). The cytoplasmic structures remain poorly developed throughout the cycle (ANCLA *et al.*, 1965; FRIEDRICH, 1967). The mitochondria are reduced in number and size, have only a few cristae (CLYMAN, 1963), and are electron-optically dense owing to changes in their membranes which contain lipids. The granular endoplasmic reticulum is extremely sparse and protein synthesis is reduced accordingly (VERHAGEN and THEMANN, 1965, 1970; TOTH *et al.*, 1972). In contrast, the cells contain abundant lipid granules.

The spotty edema of the *stroma* is striking, accentuated by the non-edematous parts composed of dense small or spindly cells (Fig. 113). The ratio of glands to stroma is shifted in favor of the stroma. Depending on the dosage of gestagen in the preparation used (see TAYMOR, 1961), a distinct predecidual or decidual change may take place prematurely (from the fifteenth to twentieth day of the cycle) and abundant granulocytes appear (Fig. 114). After therapy with 17α-hydroxy-progesterone the synthesis of DNA by the stromal cells is measurably increased (FETTIG, 1965). Ultrastructurally, the rough and smooth endoplas-

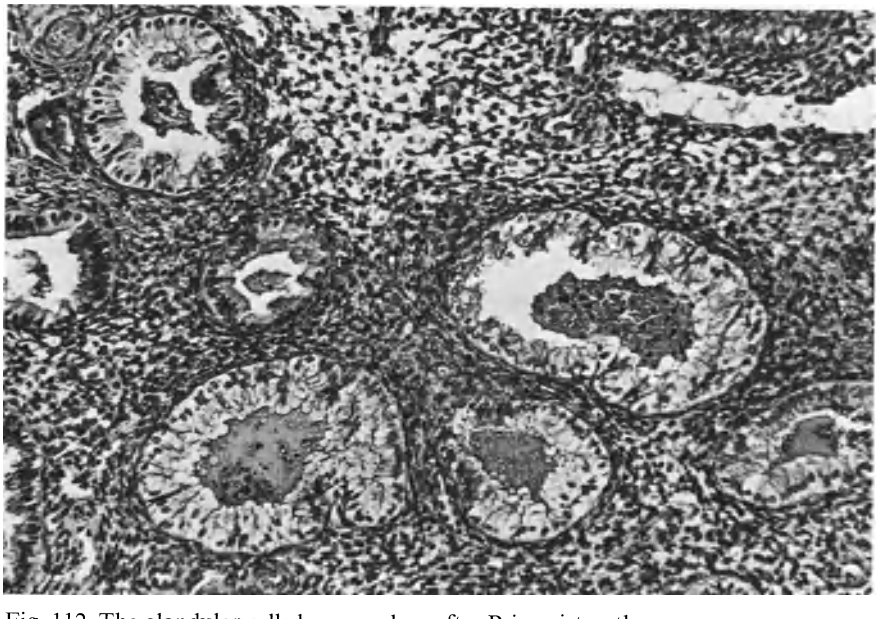


Fig. 112. The glandular cells become clear after Primosiston therapy

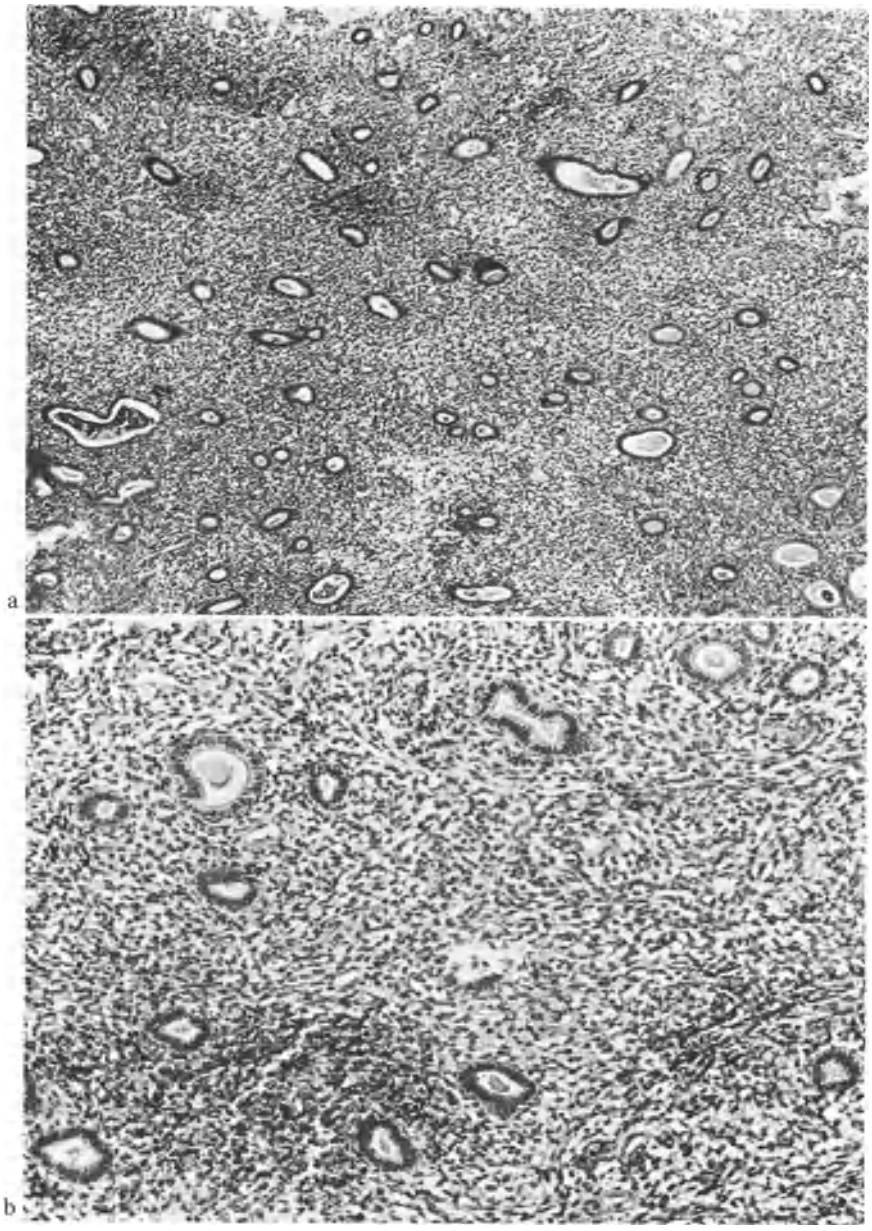


Fig. 113a and b. Beginning atrophy of the endometrium after 6 months of Anovlar. (a) Low magnification. (b) Higher magnification

mic reticulum as well as the Golgi apparatus are hyperplastic; glycogen begins to accumulate (WIENKE *et al.*, 1969). Occasionally with the breakthrough bleeding that follows decidual casts of the endometrial cavity are shed, resembling those discharged in dysmenorrhea membranacea. The differentiation of the stro-

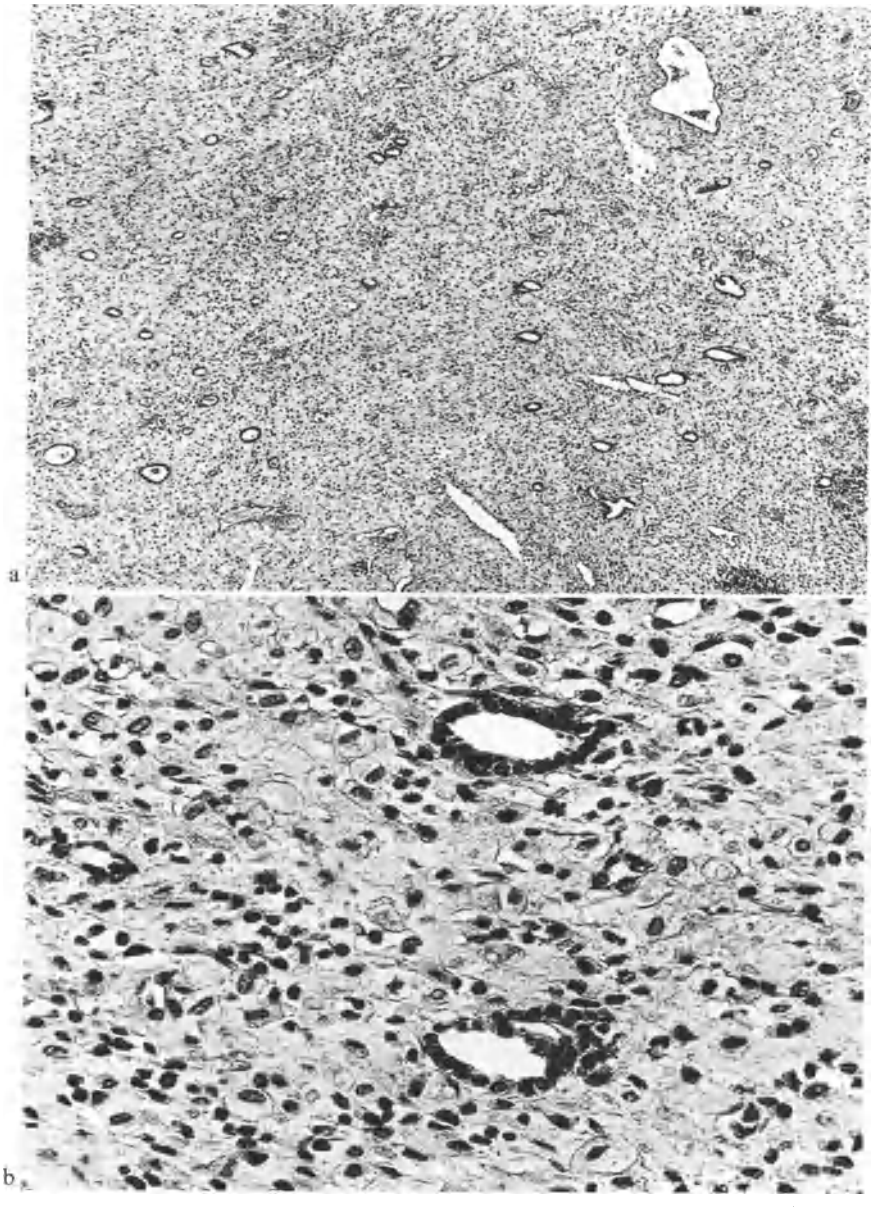


Fig. 114a and b. Arrested secretion after combined hormonal therapy, the gestagen component however predominating. The glands are strikingly small and atrophic, the stroma has undergone decidual change. (a) Low magnification, (b) high magnification

mal cells into predecidual cells and granulocytes is not always coordinated, and even regions composed of small stromal cells may contain abundant granulocytes. In other parts of the stroma the cells may exhibit no evidence of differentiation. The development of the *reticulum network* varies greatly from region to

region. Stroma containing well-formed, dense fibers may merge with stroma in which the fibers are either sparse or not demonstrable. WAIDL *et al.* (1968) drew attention to the absence of a normal reticulum network, particularly in the second half of the cycle.

The *blood vessels* undergo extraordinary changes. Generally the spiral arteries fail to develop. In their stead we find small or dilated capillaries. In rare instances a spiral artery may proliferate but does so prematurely and incompletely. The development of the vascular branchings in the superficial endometrium, especially of the subepithelial sinusoids, parallels the predecidual change of the stromal cells, and is therefore often focally intensified. ANCLA *et al.* (1965) were impressed by the proliferation of the endothelial cells in these vessels; it resembles that seen during pregnancy or that produced experimentally in the endometria of monkeys by relaxin (DALLENBACH-HELLWEG *et al.*, 1966). BLAUSTEIN *et al.* (1968) found such vascular proliferations in 48 per cent of endometria of patients taking the combination agents and in 73 per cent of them receiving sequential agents. Perhaps fluctuations in hormones stimulate the abundant granulocytes, which are found focally in the predecidually changed stroma, to release their relaxin prematurely, thus causing the endothelial cells to proliferate. Some authors (OBER *et al.*, 1964; CROWSON *et al.*, 1965; OBER, 1966, 1977) have even reported finding intense dilatation of stromal vessels and thromboses. Characteristic are small, or even large, focal hemorrhagic necroses of the stroma that probably account for the *protracted breakthrough bleeding* which often necessitates curettage. The breakthrough bleeding is a manifestation of the disturbed hormonal balance and is caused by a temporary, dose-dependent, relative or absolute deficiency of either of the two hormones administered. Accordingly, it may represent an estrogen-withdrawal bleeding like that of an anovulatory cycle, or it may represent a progesterone withdrawal bleeding with release of relaxin like that of menstruation, except it is protracted and develops focally. Because it develops so irregularly and imperfectly, the endometrium most likely does not shed normally, in some cases it may not shed at all, the retained portions merely shrinking. As a result the roughness of the endometrium is intensified. The lack of shedding may be recognized by finding slightly dilated glands filled with old inspissated blood, telltale evidence of a previous cyclic bleeding. Although most of the blood from such hemorrhages is probably discharged from the uterine cavity, some apparently seeps into patent glandular lumina of the adjacent, non-desquamated mucosa, to coagulate and remain there for long periods (cf. p. 94, Fig. 39), rarely even forming psammoma bodies (VALICENTI and PRIESTER, 1977).

The *variations* in the histological picture, which depend as already implied on the dosages and types of preparations, are readily seen electron-microscopically (FRIEDRICH, 1967). After using the combination agents the principle alterations found are the predecidual reaction and the concomitant sinusoidal dilatation of the vessels, the thromboses and the breakthrough hemorrhages. After higher doses of gestagens (5–10 mg) and after 19-nortestosterone these alterations are more intense than after using lower doses of gestagens (0.5–2 mg) and after 17α-hydroxyprogesterone acetate. As mentioned before, some synthetic gestagens are up to eighty times more active than natural progesterone (SUCHOWSKY and BALDRATTI, 1964; VOKAER, 1964; see Table 17). The frequent breakthrough bleeding after higher doses of gestagen can probably be explained by the development of many granulocytes in the predecidual stroma. With the fall of the gestagen these granulocytes liberate their relaxin, causing

dissolution of the stromal fibers. Equivalent breakthrough hemorrhages can be produced in the endometria of monkeys by hormonal means (DALLENBACH-HELLWEG *et al.*, 1966).

Therapy with *monthly injections of 17α-dehydroprogesterone and estradiol* results in proliferative changes with glandular mitoses during the first nine days of the cycle, followed by irregular and insufficient glandular secretion and predecidual stromal transformation during the remaining part of the cycle (CZERNOBILSKY *et al.*, 1969). The secretory suppression is less pronounced than with the oral combination contraceptives, although great individual variances may be observed. These may be explained by individual differences in absorption rates of both hormones from cycle to cycle.

Since such a wide spectrum of histological pictures may develop, it is obvious why an accurate *dating of the endometrium* is impossible and why the daily changes advance imperfectly. For instance, during a cycle inhibited by oral contraceptive agents we may find only minimal variations, limited principally to differences in glandular development and in extent of focal breakthrough bleeding. Basal secretory vacuoles usually appear on the seventh or eighth day of the cycle, and the secretion may reach its "maximum" by the thirteenth to fifteenth day. Thereafter the glands generally regress to a resting afunctional state. The focal predecidual reaction ordinarily either begins on the twentieth day (RYAN *et al.*, 1964; STARUP, 1967) or fails to develop (KRAUSE *et al.*, 1968). Invariably there is striking discrepancy in the development among the glands as well as between the glands and stroma.

In contrast, the *prolonged use* of contraceptive agents results in further histological changes. The abortive secretory changes gradually subside from cycle to cycle, and finally disappear (see GOLDZIEHER *et al.*, 1964; RYAN *et al.*, 1964; CROWSON *et al.*, 1965; AZZOPARDI and ZAYID, 1967; ROBEY *et al.*, 1968). In some women the *endometrium atrophies,* and with its sparse and tiny glands it is indistinguishable from that of a non-treated, castrated woman (see CHARLES, 1964; SHEFFIELD *et al.*, 1969; Figs. 115 and 116). Somewhat later the glands may disappear, or their indistinct remnants, lined by flattened endothelial-like cells, may readily be confused with capillaries. The stroma becomes poor in cells, consisting primarily of collagenous fibers. A protracted breakthrough bleeding may supervene in these atrophic endometria. Such bleeding probably is due in part to the associated atrophic changes in the walls of blood vessels, in part to the focal refractoriness of endometrial tissue for one of the hormones (receptor function lost), causing in a relative and real decrease in hormonal action locally. The secondary amenorrhea that occasionally develops in these women can easily be explained by a complete refractoriness of the endometrium to hormones (Fig. 117). We have observed several patients in whom massive doses of hormones, given to induce ovulation, failed to produce any change in the refractory endometria (see also SHERMAN, 1971; 1975), results similar to those obtained experimentally in monkeys (see HISAW and HISAW, 1961). Thus this iatrogenic atrophy differs not only histologically from the physiological atrophy of ageing but also functionally by failing to respond to treatment. Physiological atrophy always responds to hormonal therapy. In contrast, iatrogenic atrophy does not always react, perhaps because the few surviving endometrial cells are unable to produce receptors for estrogen, a result of genetic injury or mutation

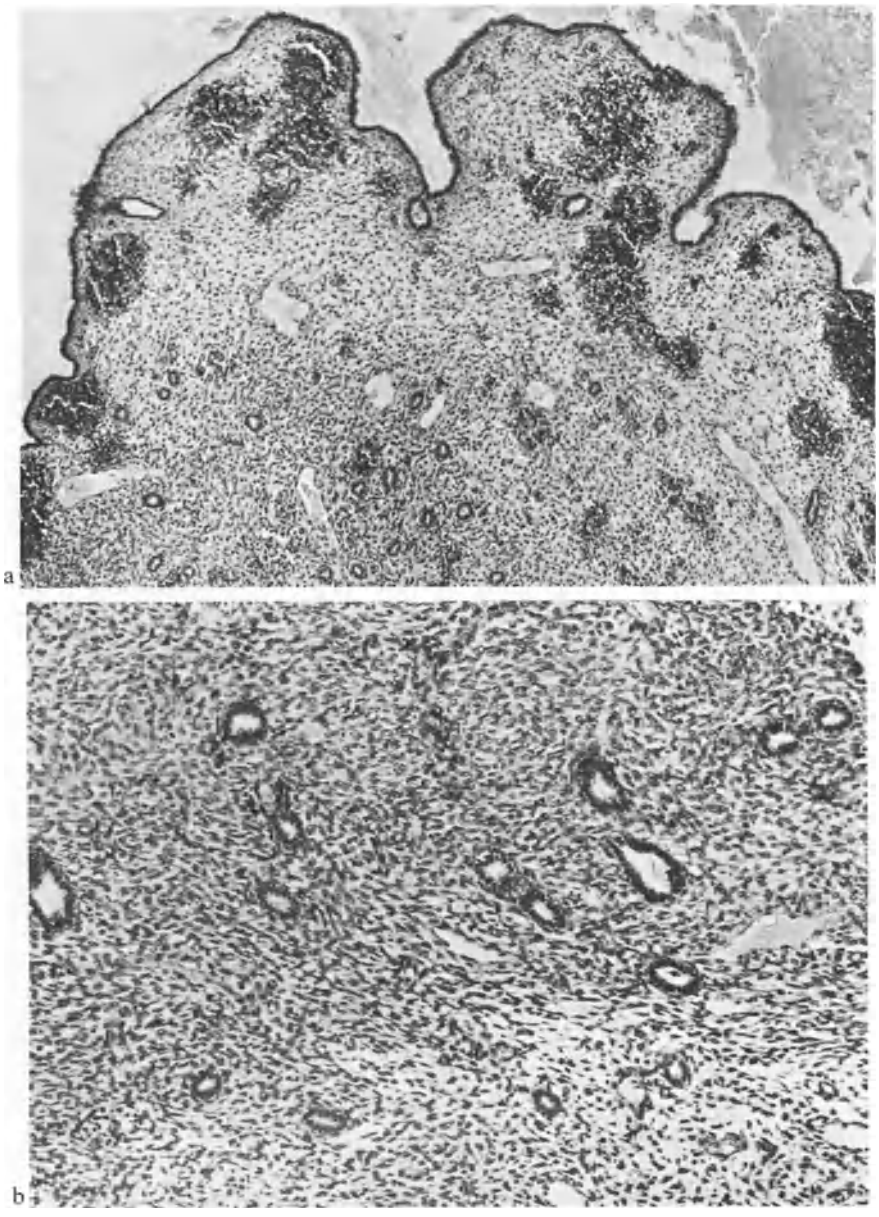


Fig. 115a and b. Advanced atrophy of the endometrium after Anovlar therapy for nine months. (a) Survey view to show irregular surface and focal withdrawal hemorrhages. (b) Higher magnification

caused by the protracted therapy with the synthetic hormones (contraceptive agents). DODEK and KOTZ (1967) have described an anovulatory syndrome developing in women after use of antifertility agents. Such extreme consequences, however, are rare, limited to single cases. Generally in atrophic endometria,

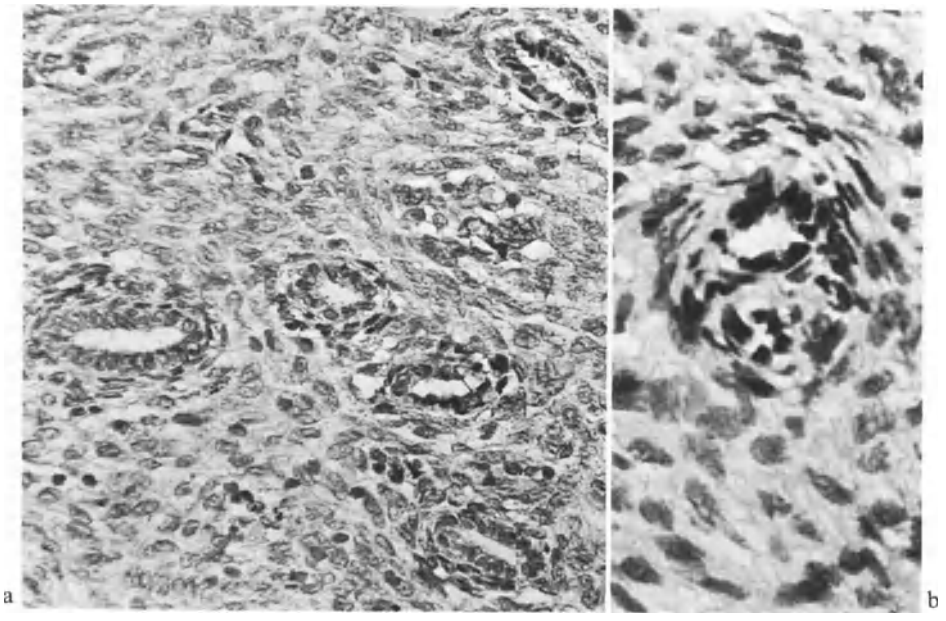


Fig. 116a and b. Same case as in Fig. 115. Some glands atrophic (a), others wasting away (b)

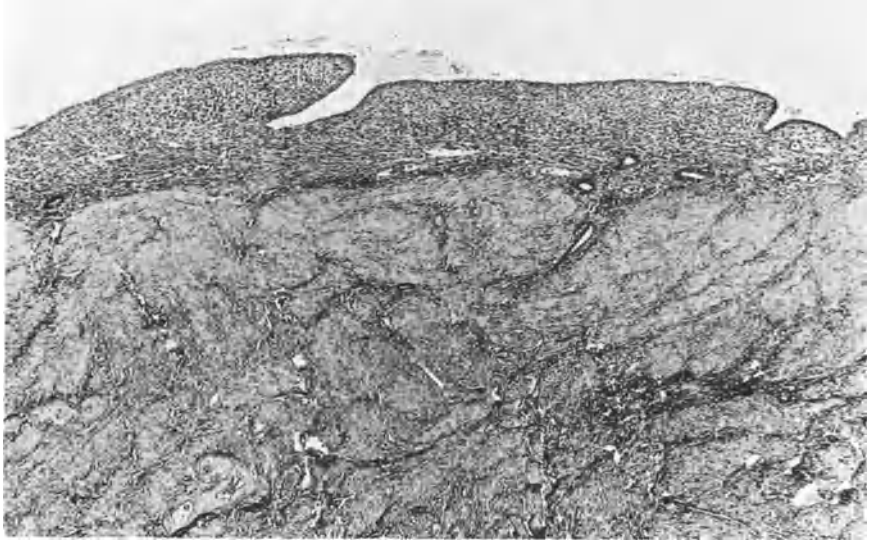


Fig. 117. Advanced atrophy of endometrium of a 41 year old patient after continuous use of oral contraceptives, combination type, for three years

between the regions without glands there are regions of reactive basal hyperplasia, from which regeneration still seems possible.—Other patients react to the long-term hormonal therapy with hyperplastic changes of the endometrial glands. That reaction may in rare instances lead to glandular-cystic (LAUFER,

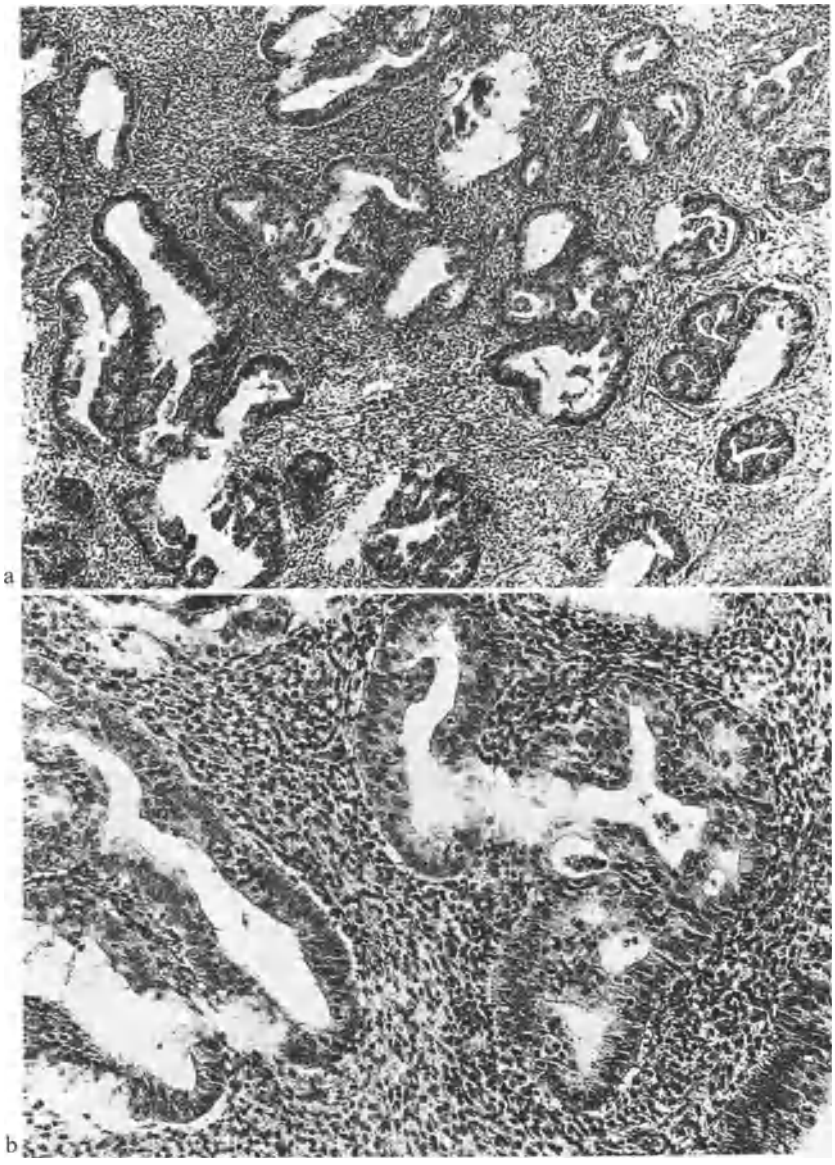


Fig. 118a and b. Beginning adenomatous hyperplasia after continuous use of oral contraceptives, combination type, for four years. (a) Low magnification, (b) high magnification

1968) or *adenomatous hyperplasia,* indicating that only the endometrial sensitivity to estrogen has persisted (or that the gestagen component of the therapy, for one reason or another, failed to exert its effect on the endometrium) (Fig. 118). Such glandular proliferation primarily develops after prolonged treatment with agents that contain high doses of estrogen, e.g., after sequential agents, or after metabolic conversion of gestagens into compounds with estrogen-

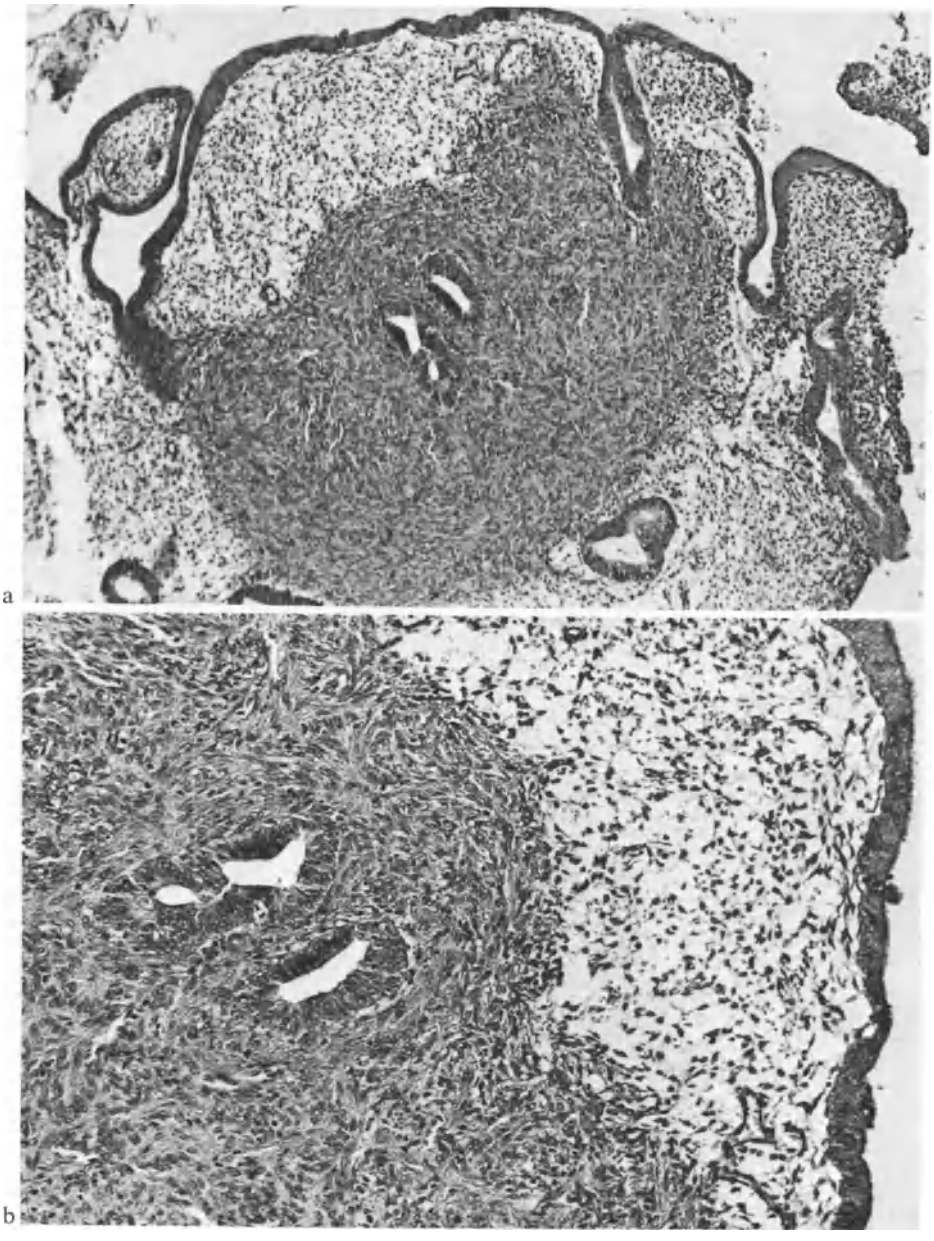


Fig. 119a and b. Focal stromal hyperplasia ("stromaloma") in a deficiently proliferated endometrium after oral contraceptives. (a) Low magnification, (b) higher magnification

ic action (CHARLES, 1964; GOLDFARB, 1964; HENZL *et al.*, 1964). Squamous metaplasia of the hyperplastic endometrial glands is occasionally observed after prolonged use of certain agents (for example, after Norethisterone) and may persist as long as four months after therapy has been stopped. SCHMID (1968)

described atypical and precancerous hyperplasia of the endometrial glands with papillary proliferation and evidence of cellular secretion after long-term therapy with "Lyndiol". Recently, increasing numbers of reports have appeared that describe invasive endometrial carcinoma arising after use of oral contraceptives with predominantly estrogen effects (see p. 187).

On the other hand, DOCKERTY *et al.* (1959) pointed out that when the gestagenic component predominates, the predecidual reaction it induces may assume a pseudosarcomatous appearance after prolonged use. Even the development of true endometrial sarcoma with pronounced nuclear pleomorphism, abundant abnormal mitoses and "positive cytology" has been observed after use of both "Norlestin" and "Provest" for three to five years (SONG *et al.*, 1970). More frequently a nodular *stromal hyperplasia* with hyperchromatic, enlarged nuclei, with excessive formation of reticulum fibers, and with capillary or arteriolar proliferation may be found in patients taking oral contraceptives (Fig. 119). These changes should not be confused with the rare presarcomatous stromal hyperplasia (cf. p. 128). What the long-term prognosis of these nodular stromal hyperplasias might be we cannot state or predict at the present. We will only learn by experience whether these hormone-induced changes will eventually evolve into the presarcomatous variety of stromal hyperplasia. If they do, then we should expect a great increase in the frequency of endometrial sarcoma in the next ten to twenty years.

Therapy with the **sequential agents** (for example, "Estirona") produces still other histological pictures, because the first progestational stimulus acts on the endometrium at a later phase of the cycle. The most prominent changes are the prolongation of the proliferative phase induced by the estrogen and the delay in the appearance of secretion. Although the secretory changes may develop uniformly, they persist as deficient. Often there is pronounced stromal edema but in spite of it the endometrium remains low, that is, its height reduced. In their rather large series of women who received sequential contraceptive agents, GOLDZIEHER *et al.* (1964) and MAQUEO *et al.* (1964) found no evidences of secretory changes by the twenty-second day of the inhibited cycle (two days after beginning the progestational agent). On the twenty-sixth day, that is, shortly before onset of withdrawal bleeding, the endometrial glands resembled those of the second day after a normal ovulation; they revealed no signs of involution. From our experience, a predecidual change usually fails to occur and endometrial granulocytes are rare. The spiral arteries remain poorly developed (BOARD and BORLAND, 1964). OBER *et al.* (1966) were able to confirm these results with the sequential type of contraceptive agents when their patients took the progestational component for only five days. In contrast, after ten days of progestational therapy (2 mg Chlormadinone daily) these investigators found a decidual reaction at the end of the sequential cycle in 10 per cent of their patients. After twenty days of such therapy the endometria of most of the women displayed a decidual reaction but the spiral arteries remained poorly developed.

Prolonged therapy with the sequential type agents leads to similar histologic changes. An endometrial atrophy, as seen with the combination agents, rarely occurs. Nevertheless, as successive biopsies will prove, the sensitivity of the endometrium (especially the glands) to the hormones gradually diminishes from cycle

to cycle. The histological pictures may show an irregular proliferation or resemble a deficient secretory phase of a moderately severe ovarian insufficiency (FETTIG and KOPECKY, 1968). Because the estrogen-effect predominates, many investigators report finding that glandular-cystic hyperplasia (up to 50%), adenomatous hyperplasia (up to 13%) and more recently endometrial carcinoma develop more frequently than with combination therapy (LYON, 1975; SILVERBERG and MAROWSKI, 1975; VANDERICK *et al.*, 1975; KELLEY *et al.*, 1976; KREUTNER *et al.*, 1976; LYON and FRISCH, 1976; COHEN and DEPPE, 1977; REEVES and KAUFMAN, 1977; SILVERBERG *et al.*, 1977). The sequential agents are less reliable contraceptives than are the combination agents; break-through ovulations occur in about 8 per cent of the women who use sequential pills (MEARS, 1965).

The effect on the endometrium of **daily small doses of a progestational agent** alone or of an injectable long-acting gestagen is more intense than that of combined preparations, and parallels that seen with gestagen treatment for endometriosis (cf. p. 222). Even during the first cycles after onset of therapy, the progestational agent severely retards the growth of the endometrium. A discordance in the development of the glands and stroma appears that varies in extent and quality, depending on the type of gestagen given, and leads to various degrees of arrested secretion.

Abortive secretion of glands may be seen as early as the 7th day of the cycle. The secretion of glycoprotein is diminished. The spiral arterioles remain underdeveloped. The reticular network appears fragmented or may not be visualized at all (KÜHNE *et al.*, 1972). Treatment with quingestanol acetate, a potent gestagen, leads to pronounced histochemical abnormalities during all phases of the menstrual cycle (FLOWERS *et al.*, 1974): diastase-resistant mucopolysaccharides accumulate at the apical border of the glandular cells. At their bases, small foci of glycogen persist throughout the secretory phase. The activities of succinic dehydrogenase, alkaline and acid phosphatases remain unaltered, suggesting that the transport ability of the epithelial cells is little affected. The cyclic variations in the acid mucosubstances also remain normal: the sulfomucins predominate during the proliferative phase and the carboxylmucins during the secretory phase. The endometrial blood vessels contain aggregates of platelets, which are PAS positive and diastase-resistant.

Pronounced changes also become apparent in the ultrastructure of glandular cells, which reveal signs of disturbed and premature differentiation and degeneration with elongated mitochondria, of irregularly developed endoplasmic reticulum, and of partial loss of the intranucleolar channel system during the secretory phase (FERIA-VELASCO *et al.*, 1972; FLOWERS *et al.*, 1974; MARUFFO *et al.*, 1974). Many cells reveal abundant tonofilaments and microtubules associated with increases in ribosomes and granular endoplasmic reticulum. These suggest that the organelles needed for glycogen synthesis and transport are present, yet the amounts of glycoprotein and the transport systems within the cells are abnormal. After a single injection of medroxyprogesterone acetate, these changes are still reversible within 90 days (ROBERTS *et al.*, 1975). – Endometrial atrophy usually ensues earlier during continuous treatment with these progestational agents than with the combination type of contraceptives (LEE, 1969; KHOO *et al.*, 1971). That is why a curettage usually proves unsuccessful, providing little to no tissue for histologic examination.

Hence, contrary to previous assumptions these agents do have an effect on the endometrium and on pituitary or ovarian function (MOGHISSI *et al.*, 1973). In some of the patients taking low doses of gestagens, ovulation and fertilization may take place. The alteration of the endometrial architecture, however, renders normal placentation impossible, resulting in spontaneous abortion, primarily because of the underdeveloped decidua. A defective development of the blastocyst may also be regarded as a direct effect of the gestagen on the fertilized ovum (cf. p. 260). In addition, since peristaltic movement and secretory activity of the fallopian tubes are decreased (MALL-HAEFELI *et al.*, 1976), there is a 2- to 5-fold risk of ectopic pregnancy (LIUKKO *et al.*, 1977). In other patients chlormadinone has been noted to inhibit ovulation. Norgestrel almost regularly inhibits ovulation, and in addition alters endometrial structure, cervical mucus and hypothalamic-pituitary function (MOGHISSI and MARKS, 1971); norethindrone acetate has a similar effect (MOGHISSI and SYNER, 1975). The depression of gonadotropin secretion may well explain the persistent endometrial atrophy and subsequent amenorrhea these patients experience during and after treatment (COUTINHO *et al.*, 1966; HASPELS, 1970).

The contraceptive steroid *R2323,* which competes for the progesterone receptor, has an effect on the endometrium like that of progestational agents (AZADIAN-BOULANGER *et al.*, 1976). The nucleolar channel system of the glandular epithelial cells remains rudimentary, giant mitochondria do not develop, and degradation of the glycogen granules by ergastoplasmic enzymes is delayed, resulting in a deficiency in glycoprotein secretion; all these signs point to progesterone insufficiency.

In monkeys the administration of estrogens after sexual intercourse (**"postcoital pills"**) delays the appearance of secretory changes in the endometrium only slightly (MORRIS and VAN WAGENEN, 1966). Apparently these pills act as contraceptives not only by effects they have on the endometrium but by their stimulation of muscular activity in the fallopian tubes and uterus, thereby preventing nidation. The effectiveness of postcoital estrogens in women apparently depends on strict adherence to proper dose, which must be about 100 times that of the usual contraceptive pill, and to proper time schedules (BLYE, 1973; HASPELS and ANDRIESSE, 1973; SHEARMAN, 1973). As to be expected, the endometrial epithelium proliferates intensely (HASPELS *et al.*, 1977) and the differentiation of glands and stroma is retarded by 5 days (VAN SANTEN and HASPELS, 1980). This retardation most likely explains how postcoital estrogen acts, disturbing the synchrony between blastocyst and endometrium (BEIER, 1981). – The gestagenic "postcoital pills" produce severe side-effects and often prove ineffective (LARRANGA *et al.*, 1975).

Enzyme-histochemical studies (CONNELL *et al.*, 1967; HESTER *et al.*, 1968) give results that in part vary considerably from those of a normal cycle. After therapy with the combination type of contraceptive agents the activity of alkaline phosphatase is only slightly reduced; after sequential therapy it develops late, analogous to the other morphological changes. It finally increases in the second half of the cycle and reaches its maximum shortly before breakthrough bleeding starts. The concentration of the acid phosphatase, however, is reduced in both of the inhibited halves of the cycle. The succinic acid and lactic acid dehydrogenases as well as carbonic anhydrase are decreased, showing only slight fluctuations during the cycle. After therapy with the combination agents the activity of β-glucuronidase is lacking; after sequential therapy it is extremely low.

When added to the culture medium, oral contraceptive agents induce changes in human endometrium cultured *in vitro* similar to those produced by the natural hormones (CSERMELY *et al.*, 1971).

Diagnostically it is difficult to classify these endometria, especially those after combination therapy. Nonetheless, the histological pictures are so characteristically abnormal, that with experience it is easy to recognize at a glance an endometrium from an inhibited cycle without knowing that the patient had taken contraceptive agents. We know of no endogenous endocrine abnormalities that are able to induce the same histological pictures. On the other hand, a conscientious pathologist endeavors to define the histological changes as precisely as possible, since from the degree of proliferative or secretory changes he finds he can draw important conclusions about the extent of hormonally-induced alterations that have developed. These conclusions, in turn, provide clues for the prognosis and subsequent treatment. Accordingly, we classify the endometrium of an inhibited cycle under a numerical code in our diagnostic decimal system (see Table 3). An "ov" behind the two-digit number points to previous anti-ovulation therapy, thus with special ov-registery cards we can easily cull these cases from the files at any time, although their numbers vary. The numbers used most often are those for the deficient, shortened or irregular proliferative and secretory phases, and those for the atrophic endometrium or the anovulatory breakthrough bleeding. At times one finds the histological picture of an irregular shedding, which by the absence of endometrial granulocytes can be distinguished from irregular shedding due to other causes (DALLENBACH-HELLWEG and BORNEBUSCH, 1969). If the estrogenic component predominates or the progestin is converted into estrogenic substances, a glandular-cystic hyperplasia results, occasionally even an adenomatous hyperplasia.

Resumption of fertility after discontinuation of contraceptives: If therapy with the contraceptive agents is discontinued in good time or at least interrupted periodically, a return to normal cycles and a normal histology is quite possible (MAQUEO *et al.*, 1963; RICE-WRAY *et al.*, 1963; MEARS, 1965; BREINL and WARNECKE, 1967). Such restoration usually occurs in 91 per cent of the women after an amenorrhea that may have lasted up to four months. The remaining 9 per cent either experience longer periods of amenorrhea (RICE-WRAY *et al.*, 1967) even up to 42 months (PLATE, 1971; INGERSLEV *et al.*, 1976) or the histological picture of a deficient secretory phase persists unchanged. The chemical composition of the contraceptive agent used greatly influences the duration of post-contraceptive amenorrhea (FERIN, 1964). The injectable contraceptive agents (SCOMMEGNA *et al.*, 1970) and the depot-gestagens (GARDNER and MISHELL, 1970; MAQUEO *et al.*, 1970) produce the longest suppression of menstruation. In addition, women experiencing menstrual irregularities prior to taking oral contraceptives are more likely to develop prolonged amenorrhea (GOLDITCH, 1972; RIFKIN *et al.*, 1972; BUTTRAM *et al.*, 1974). The cause of such amenorrhea may be either anovulation from hypothalamic, pituitary or ovarian injury or endometrial atrophy and refractoriness. The occasional occurrence of amenorrhea with galactorrhea after oral contraception is thought to point to a depression of hypothalamic function, resulting in a prolonged decrease in the formation

or secretion of pituitary gonadotropins (FRIEDMAN and GOLDFIEN, 1969; HALBERT and CHRISTIAN, 1969; STARUP, 1972).

Mode of action. The question of how the antifertility agents function has led in the last years to the formulation of countless theories. As yet no one has provided a definitive answer. Most probably many factors are important. These may vary from patient to patient and may depend in part on the type of therapy, on the composition of the agent, and on the dosage of hormones used; then too, all of these factors may act either together or independently. It has been possible to prove that the contraceptive agents inhibit ovulation in some women (RAUSCHER and LEEB, 1965) but such inhibition does not seem to be essential for the contraceptive effect.

The *structural changes induced in the histology of the endometrium* of most patients would be enough to explain the contraceptive action. As we have already observed during the discussion of functional disturbances, an endometrium morphologically modified by disturbed hormonal regulation becomes functionally altered as well, and is quite unable to accept or support a fertilized ovum. Numerous investigators have studied changes in various structures of the endometrium and concluded, these alterations were responsible for preventing nidation. HALLER (1966) referred to regressive changes in glands at the time of implantation; GOLDZIEHER *et al.* (1962), GOLDZIEHER and RICE-WRAY (1966), HESTER *et al.* (1968) emphasized the extensive atrophy of the endometrium; OBER (1966) pointed to the faulty development of the spiral arteries; WAIDL *et al.* (1968) stressed the inhibited development of intercellular fibers needed for supporting the blastocyst; HACKL (1968) was able to demonstrate that the glucose metabolism of the endometrium was reduced *in vitro,* and suggested that a similar change *in vivo* might be important. MORRIS (1973) considered the reduced endometrial anhydrase activity to be the basic mechanism of action. Furthermore, the inhibited development and ultimate incomplete maturation of the endometrium induced by the sequential agents, a state equivalent to a deficient secretory phase, undoubtedly is enough to prevent nidation (FETTIG and KOPECKY, 1968; KALTENBACH *et al.*, 1973).—Clinical studies have repeatedly shown that *the excretion of urinary gonadotropins is decreased* (EPSTEIN *et al.*, 1958; BUCHHOLZ *et al.,* 1962; DEMOL and FERIN, 1964; WALSER *et al.,* 1964; KAISER *et al.,* 1966). With the combination agents the mid-cycle peak of LH, which normally induces ovulation, usually is flattened (BUCHHOLZ and NOCKE, 1965). With the sequential agents it is chiefly the FSH that is decreased; the peak of LH remains unaffected (SWERDLOFF and ODELL, 1968). Apparently the estrogenic component of the contraceptives suppresses the secretion of FSH (VORYS *et al.*, 1965), whereas the progestins inhibit the production of LH (DICZFALUSY, 1968; DICZFALUSY *et al.*, 1969). In response to the fall of gonadotropins the ovaries begin to atrophy, as is readily evident from the increase in their stroma (fibrosis) and the failure of the Graafian follicles to mature. From these facts it seems most likely the contraceptive agents suppress ovulation by way of a feed-back mechanism on the pituitary and hypothalamus (see also ARTNER and KRATOCHWIL, 1965). We know from experiments in animals that the hypophysis enlarges, the chromophobe cells increase in number, and the acidophils and basophils lose their granules (BORELL, 1966). From the studies of LUNENFELD (1964), however, it seems the

contraceptive agents also *act directly on the ovaries by inhibiting certain enzyme-systems.*—Additional investigators indicate that other preparations may still be effective contraceptive agents although they fail to suppress ovulation (GOLDZIEHER *et al.*, 1962; ERB and LUDWIG, 1965). In such instances, especially after continuous administration of minute doses of progestins, the contraceptive effect is attributed in part to the endometrial disturbance (KÜHNE *et al.*, 1972), in part to the *altered composition and increased viscosity of the cervical mucus* that retards passage of the sperm up the endocervical canal (HALLER, 1966; GARCIA, 1967). Then too, some investigators believe these altered cervical secretions prevent *the sperm* from acquiring the capacity to fertilize (TAUSK, 1969). Apparently the sperm need to stay at least six hours in the female genital tract to allow enzymes from the uterine mucosa to digest a protective coating on them before they are able to fertilize. Contraceptive agents also act on the *fallopian tubes,* affecting the secretory cycle of their epithelium, the size of their lumen, and the contractions of their musculature (see Table 19).

The histological changes found in the endometrium after use of contraceptive agents are informative for many reasons. On the one hand, the changes give us unique insight into how normal and abnormal endometria react to hormones; on the other hand, the changes show us what the limits of these reactions are.

Table 19. Probable mechanisms of action of the oral contraceptive agents

Composition of the Pill	Combination Type of Pill		Sequential Type of Pill		Pure Progestational Pill	
	Progestin + medium dose of estrogen	Progestin + high dose of estrogen	High dose of estrogen	Estrogen + progestin	Small doses of progestins ("luteal supplementation")	
Used—on days of the cycle	5–24 5–25 5–26	5–24 5–25	5–19 + 20–24 5–20 + 21–25 5–14 + 15–25		5–24	continuously
Inhibition of the Gonadotropin	LH	LH (+FSH?)	FSH (+LH?)		None or irregularly	None or irregularly
Effect on the Ovarian Enzyme Systems	Possible	Possible	?	?	?	
Endometrial Factor	++	++	+	+	++	++
Cervical Factor	++	++	none	+	++	++
Contractions of Fallopian Tube	depressed	depressed	increased	?	depressed	depressed

Like every other organ or tissue of the body, the endometrium changes its mode of reaction, depending on the duration, intensity, and type of stimulus affecting it. As experiments in monkeys carried out continuously for many years showed, the endometrium has, as HISAW so cogently expressed it, "a memory like an elephant", that is, it never forgets previous hormone therapy and reacts later accordingly. Long-term studies of human endometrium have been made after protracted therapy with contraceptive agents. The results suggest that because of injury to specific genomes the endometrial cells gradually lose their sensitivity to hormones and eventually atrophy or they remain responsive only to estrogen. Even though all of these changes may be reversible in a majority of patients after therapy is stopped, the very fact some changes are irreversible in a small percentage of women should cause concern. Accordingly, from the standpoint of the pathologist it hardly seems justified for young healthy women to use contraceptive agents before their first pregnancy. If, however, a woman wishes no more children, then such doubts seem less warranted. A discussion of the numerous deleterious consequences of hormonal therapy observed clinically, although important, are not pertinent to our subject at hand.

From our present knowledge of the action of hormones on the endometrium, we can formulate the following hypothesis about the possible late consequences of a continuous, truly long-term therapy:

1. By binding to specific receptors in their target cells, *estrogens* activate genomes, thereby inducing mitosis and cellular proliferation. From these facts several possibilities may occur:

a) during a normal cycle progesterone causes estrogen-primed target cells to differentiate, inhibiting further growth,

b) continuous, unopposed estrogen in small or moderate doses may lead to *uninhibited growth* (glandular-cystic hyperplasia → adenomatous hyperplasia →eventual carcinoma, see HERTZ, 1968),

c) prolonged large doses of estrogen may injure the target cells and destroy their ability to produce receptors, terminating in atrophy of the endometrium (as proven by animal experiments).

2. *Progesterone* acts on the target cells to stimulate their differentiation and to suppress their uptake of estrogen:

a) in physiological doses it induces the target cells to differentiate, thereby inhibiting their proliferation,

b) when the progesterone-effect predominates continuously (its dosage is unimportant) the action of estrogen is persistently blocked, and the endometrium eventually undergoes irreversible *atrophy*.

Fortunately the modern combination preparations with their greatly reduced concentrations of hormones rarely induce the adverse reactions described, and if reactions do occur they are less severe. It should be emphasized, that these adverse reactions appear only when the patient's hormonal balance is profoundly upset. If the pathologist knows about them, it is he who generally recognizes them first. A precise histological diagnosis of the changes and their causes (from estrogens or gestagens?) is of paramount importance. From the kind of endometrial abnormalities he sees, the pathologist can provide the gynecologist with important information on how to treat the patient with another hormon-

al preparation, whose composition is deemed right for bringing about hormonal balance.

The **endocervical mucosa,** portions of which are often included in curettings (see p. 16), reacts to hormone therapy quite differently from the endometrium. Estrogens alone have very little if any effect on the endocervical glands but may induce squamous cell metaplasia of the surface epithelium. In contrast, gestagens alone call forth an excessive adenomatous or intraluminal proliferation of the endocervical glands (Fig. 120a). Often the reserve cells proliferate luxuriantly as well (Fig. 120b). The adenomatous hyperplasia of the endocervical glands closely resembles the glandular hyperplasia evoked in the corpus endometrium by estrogen, but surpasses by far the hyperplasia induced by excessive endogenous stimulation with progesterone, as for instance, during pregnancy. When both hormones are given, the changes brought about by the gestagens usually predominate. Since intensive therapy with gestagens leads to endometrial atrophy, such curettings may consist almost exclusively of large portions of hyperplastic endocervical mucosa with only tiny fragments of atrophic endometrium.

ε) Treatment with Gonadotropins. In the monkey (HISAW, 1944) and in humans chorionic gonadotropin (HCG) alters the menstrual cycle by prolonging the secretory phase. The corpus luteum persists. More relaxin is produced, as the proliferating endothelial cells of small stromal vessels and the deciduomata indicate. Treatment of hypogonadotropic ovarian insufficiency with hypophyseal gonadotropin (HHG), however, has proved worthwhile. By giving their patients 400 units a day for ten to fourteen days, BETTENDORF and BRECKWOLDT (1964) succeeded in inducing follicles to mature and to ovulate. For stimulating the maturation of follicles, other authors (VAN DE WIELE and TURKSOY, 1965; SCHMIDT-ELMENDORFF and KAISER, 1967) pretreated with menopausal gonadotropin (HMG), then administered HCG (4000–5000 i.U.) to bring about the ovulation. In one large series of patients, 91 per cent of the women ovulated and 51 per cent became pregnant (LUNENFELD, 1965). Occasionally, several follicles may mature and ovulate at the same time, resulting in multiple pregnancies (GEMZELL, 1966). The endometrium may undergo partial secretory changes (see BUXTON and HERRMANN, 1961), whereby some of its overstimulated glandular cells may develop such large polygonal nuclei and swollen, clear cytoplasm that they resemble cells of the Arias-Stella phenomenon (Fig. 127). The longer HHG is continuously given, the more intense these abnormal changes become.

Clomiphene is also useful for regulating the length of the cycle and for inducing ovulation (GREENBLATT *et al.*, 1961) (50 mg daily until the basal temperature rises or 100–150 mg daily for five days; KISTNER, 1965). In fact, it often proves effective (especially then) when previous treatment with gonadotropin failed (DÖRING, 1965). In contrast, in primary hypogonadotropic ovarian insufficiency it has no effect (BETTENDORF *et al.*, 1965). To decide which drug should be used, either the "progesterone test" can be performed or a measurement made of the urinary estrogens before therapy is started. If the progesterone test is negative or the urinary excretion of estrogen for 24 hr is below 10 μg, then gonadotropin should be administered. If the progesterone test is positive or the hourly value for urinary estrogens exceeds 10 μg, then clomiphene is the drug of choice. That would suggest that clomiphene most likely affects the

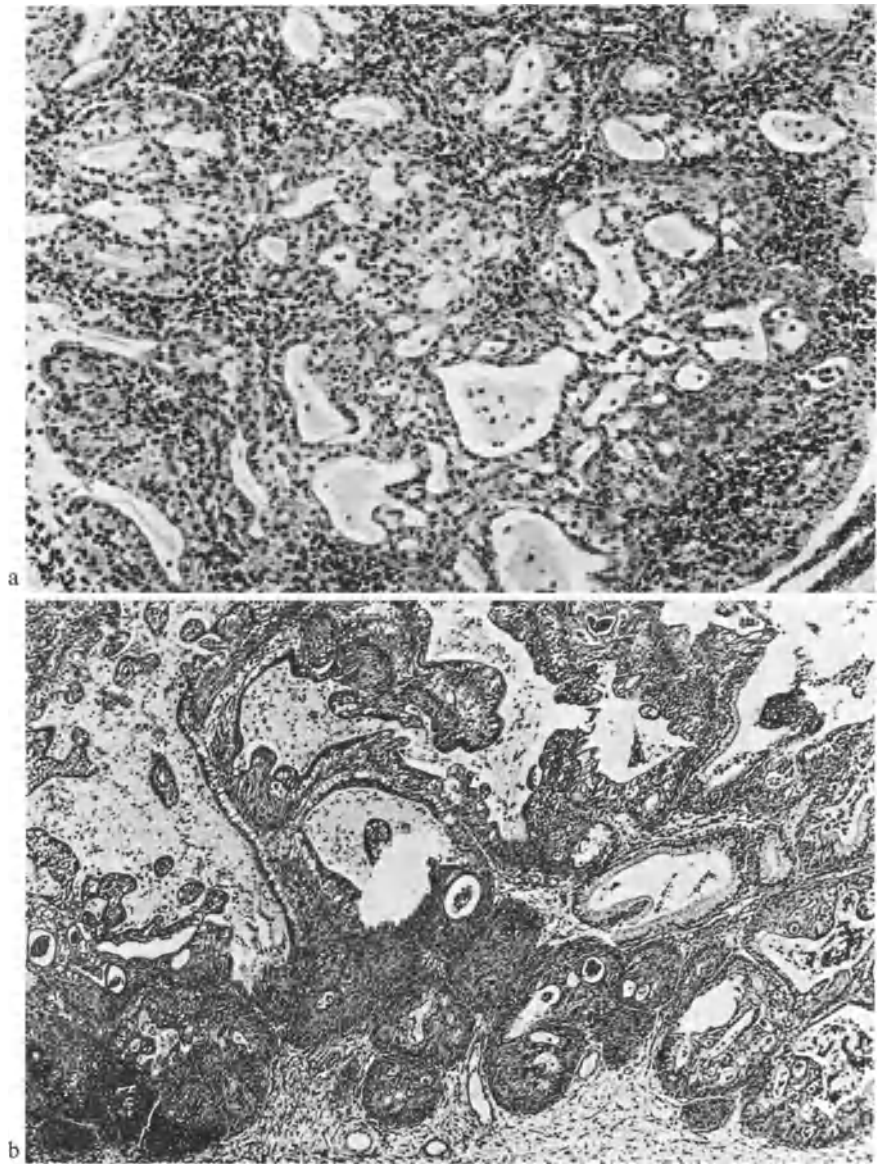


Fig. 120 a and b. Adenomatous hyperplasia of the endocervical mucosa. (a) Proliferation and branching of glands as small alveoli formed by poorly differentiated glandular epithelium. (b) Where glands confront stroma an excessive hyperplasia of reserve cells develops

ovary directly and is able to induce ovulation only when the controlling hypophyseal centers are normal, as for example, in a normogonadotropic ovarian insufficiency caused by the Stein-Leventhal syndrome. About 70–80 per cent of the amenorrheic patients treated ovulate, particularly those with the Stein-Leventhal syndrome. Ovulation usually occurs within two to forty-one days after onset

of treatment; in more than 50 per cent of the patients it occurs within two weeks. The percentage of patients that become pregnant varies widely (WHITELAW *et al.*, 1964; DÖRING, 1965; CHARLES *et al.*, 1967; TAUBERT, 1969). The average, however, is about 20 per cent. If HCG and clomiphene are given together (COX *et al.*, 1968), or if the dose of clomiphene is increased (GORLITSKY *et al.*, 1978), then about 50 per cent of the patients become pregnant. An endometrium anovulatory before treatment with clomiphene histologically shows after treatment a secretory change resembling that of a normal cycle (CHARLES *et al.*, 1963). Only about 20 per cent of the women so treated develop a full secretory change; in the others the change remains incomplete (VAN HALL and MASTBOOM, 1969). These investigators explain the discrepancy between the frequency of ovulation and that of pregnancy by postulating pseudoovulations due to luteinization of thecal cells of an unruptured follicle. A biphasic curve of the basal (body) temperature may result as well and be misconstrued as a sign of ovulation. Although the basal temperature rises, the endometrium may remain unresponsive and non-secreting because of its primary, inherent refractoriness to ovulatory stimulation (cf. Table 6, p. 97; WHITELAW *et al.*, 1970). Karyotypic studies of women after clomiphene therapy revealed an increase in heteroploidy and in chromosomal aberrations of endometrial tissue, results that explain the persistant infertility of some of those patients (CHARLES *et al.*, 1973).

Clomiphene stimulates the ovaries and adrenal glands to synthesize more estrogen (PILDES, 1965) by acting directly on the enzymes (particularly 3β-oldehydrogenase) needed for converting the steroids (CARLSTRÖM and FURUHJELM, 1969). Furthermore, because clomiphene chemically is similar to the synthetic estrogen TACE (chlorotrianisene), it binds to the estrogen receptors of the target cells, preventing the natural estrogens from binding. These then accumulate and by means of a feed-back mechanism stimulate the anterior pituitary to secrete more gonadotropins (primarily FSH) (BUHL-JØRGENSEN *et al.*, 1976). Thus, depending upon its dose and how long it is administered, clomiphene may act as estrogen or as an antiestrogen. It may be used, therefore, not only to induce ovulation but also in large doses (200–400 mg daily for from one month to two years; WALL *et al.*, 1964, 1965) to treat glandular-cystic hyperplasia and endometrial carcinoma after the menopause. Such intense therapy, like therapy with progesterone, serves to block the estrogen receptors, leading to a secretory change of the adenomatous or carcinomatous glands, and to their regression in some patients (KISTNER, 1965). If the Graafian follicles still possess the potential to mature and ovulate, then continuous treatment with clomiphene (100–200 mg daily) will induce a secretory phase that may last six to eight weeks. The stroma will show a definite, predecidual change. If therapy is continued without a pause, the endometrium gradually atrophies (KISTNER *et al.*, 1966). In summary we must frankly admit that some of the details of how clomiphene acts remain unexplained (see LORAINE and BELL, 1968).

The **antigonadotropin** Danazol, a derivative of 17α-ethinyl testosterone used for treating endometriosis, inhibits centrally the secretion of FSH and LH. Consequently, ovarian function dwindles and the endometrium becomes atrophic (DMOWSKI and COHEN, 1975).

With **Retrosteroid,** a new agent capable of inducing ovulation and related to dydrogesterone, HERZER *et al.* (1969) were able to induce focal secretory changes only in the endometrial

glands; the stroma remained unchanged. Even more remarkable, the drug produced that effect only during anovulatory cycles or after the menopause. In women with normal menstrual periods it focally stimulated the proliferative changes and inhibited the secretory changes.

The study of the effects and uses of **prostaglandins** has received much attention in recent years. These agents are best measured by biochemical techniques. It would go beyond the purpose of this monograph to review the vast literature on prostaglandins; we refer the reader to special articles dealing with them.

b) After Intrauterine Contraceptive Device

The intrauterine device as a contraceptive is not new. RICHTER (1909) and GRÄFENBERG (1931) first reported on the use of intrauterine rings or spirals for preventing pregnancy. Although these devices proved effective, they became unpopular because of the infections they induced. When it became apparent, however, that the oral contraceptive pills were not the ideal means for birth-control among analphabetic peoples, the intrauterine device came under study again. In the early 1960's various designs of loops and coils made of plastics were devised and tested (MARGULIS-coil, LIPPES-loop, DALCON-shield). These were easy to insert compared with the ring device but proved unsatisfactory because of higher rates of pregnancy, expulsion and other complications. Consequently, in addition to these "inert" types, medicated progesterone- and copper-"T"-devices have been designed for adding local hormonal or chemical effects to the mechanical irritation of the devices. These have in general proved most effective in their protection against pregnancy. They also produce far fewer side-effects than the rings, coils and loops (Fig. 121).

The histologic reaction of the endometrium to the device varies with the type used. In the immediate vicinity of the **inert devices** the functional development of the endometrium is usually accelerated; electron-microscopic studies generally reveal premature secretory changes. During the proliferative phase giant mitochondria appear in the epithelial cells of the glands. Directly after ovulation the stromal cells undergo predecidual change (WYNN, 1967, 1968). Mechanical injury of the endometrium often leads to decidualization of the surrounding stroma, not only in the experimental animal (for example, deciduoma of the rat) but also in women (SCHILLER, 1925). Since one would expect a firm foreign body like an intrauterine device to injure the endometrium, it was not surprising when numerous histological studies revealed that these devices also induced focal decidualization (see illustrations of HALL *et al.*, 1965, and WILSON *et al.*, 1965; TAMADA *et al.*, 1967). In about half of the women that change is already evident at the time of ovulation, and occasionally the dilated sinusoids of capillaries, so characteristic of the decidua, are also present (Fig. 122a). Even an Arias-Stella-phenomenon may occur (HALL *et al.*, 1965). In other instances, glandular development may be focally retarded but stromal differentiation advanced (NICOLAISEN *et al.*, 1973). The endometrium directly beneath the device may show a pressure atrophy with focal fibrosis under the thinned surface epithelium (BONNEY *et al.*, 1966). Large regions of surrounding endometrium may go unaffected and develop normally (KWAK, 1965; ROZIN *et al.*, 1967).—The endometrium adjacent to the device may contain sparse or rarely heavy infiltrates of leucocytes, lympho-

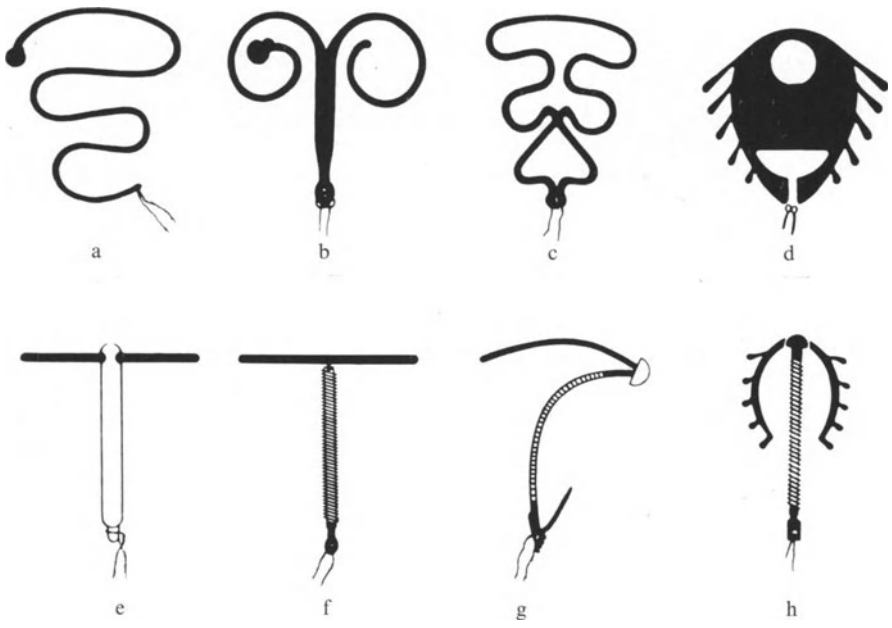


Fig. 121a–h. The various generations of intrauterine devices. Upper row: action purely mechanical. (a) Lippes Loop (b) Saf-T-Coil, (c) Dana Super, (d) Dalcon Shield. Lower row: forms bearing medications. (e) Biograviplan containing gestagen, (f) Copper-T (Gyne-T), (g) Copper-7 (Gravigard), (h) Multiload

cytes and plasma cells, which may persist for many months even in the absence of bacterial infection (MOYER and MISHELL, 1971). Leucocytes may also fill the glandular lumina beneath the surface. Some investigators have also found bacteria in the early stages (POTTS and PEARSON, 1967). Occasionally there is a foreign body reaction with giant cells (BORELL, 1966). We found the inflammation less pronounced following use of the DALCON shield than with the original loop and coil devices. In the regions involved by the inflammatory reaction the endometrial differentiation may be retarded, giving the false impression of a generally retarded secretory phase (LEE *et al.*, 1967). In their studies ANCLA *et al.* (1967) described microthrombi of agglutinated platelets in small stromal capillaries. Histochemically, the endometria of women using the intrauterine device reveal no significant variations in enzyme reactions or in contents of nucleic acids and glycogen (KWAK, 1965; SHAHANI *et al.*, 1967), but acid mucins may increase throughout the menstrual cycle (HESTER *et al.*, 1970).—A small percentage of the women using the intrauterine device develop a glandular-cystic or adenomatous hyperplasia, at times with extensive squamous metaplasia of the glandular and superficial epithelia. OBER *et al.* (1968) reported an adenocarcinoma occurring 57 months after insertion of an intrauterine device composed of polyethylene.

The premature secretory and decidual-like changes are reasons enough to explain the contraceptive action of the inert intrauterine devices. We know from experience that a decidual change, as well as any alteration in the hormonal synchrony of the endometrium, alone suffices to prevent implantation of the

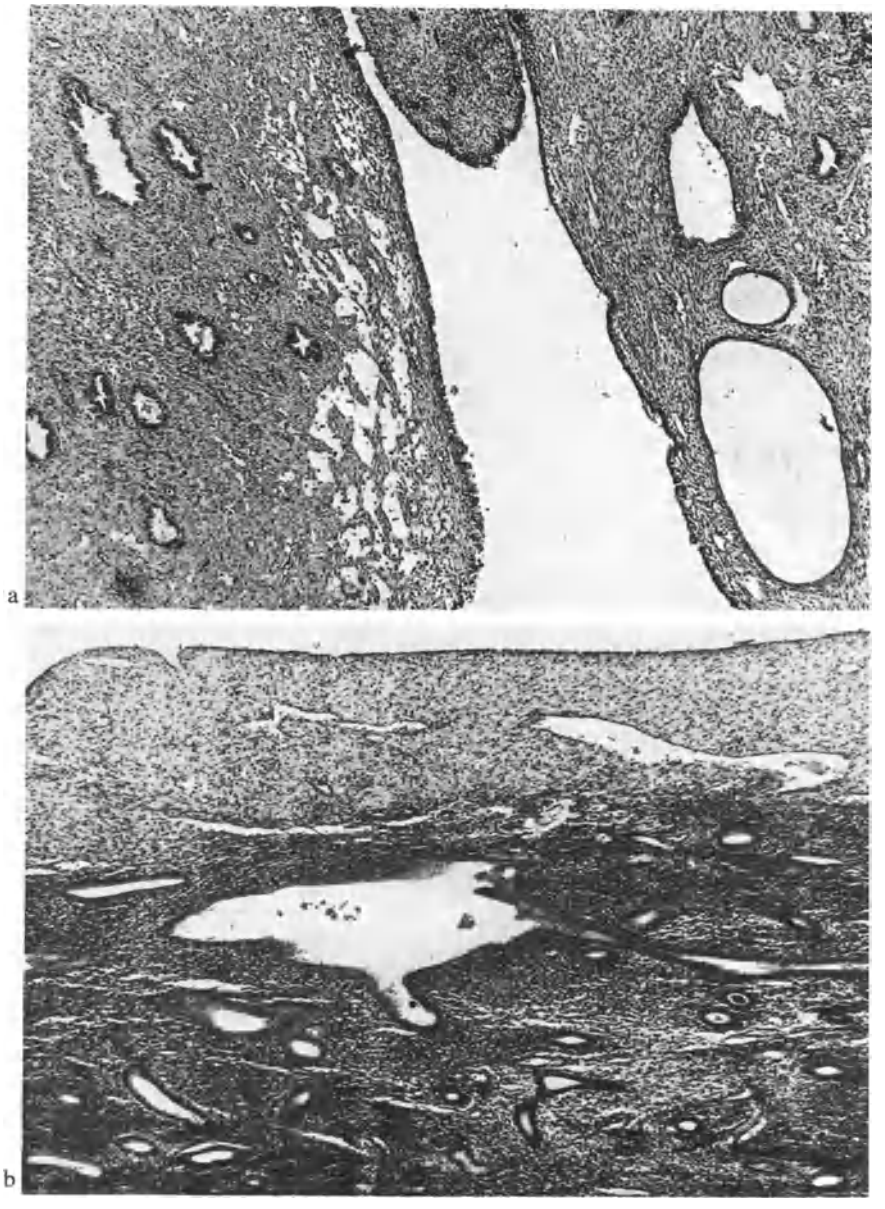


Fig. 122 a–c. Endometrium after intrauterine contraceptive device (IUD). (a) Inert device: mechanically induced focal decidual change of stroma (at the left) with secretory glands (cf. Table 20). At the right, the opposing endometrium consists of a fibrous stroma and cystically dilated glands. (b) Medicated device (containing gestagen): focal superficial arrested secretion with decidual change of stroma and atrophic glands. The underlying endometrium normally proliferative. Note the sharp line between the two layers. (c) Higher magnification of (b). (c) See page 250

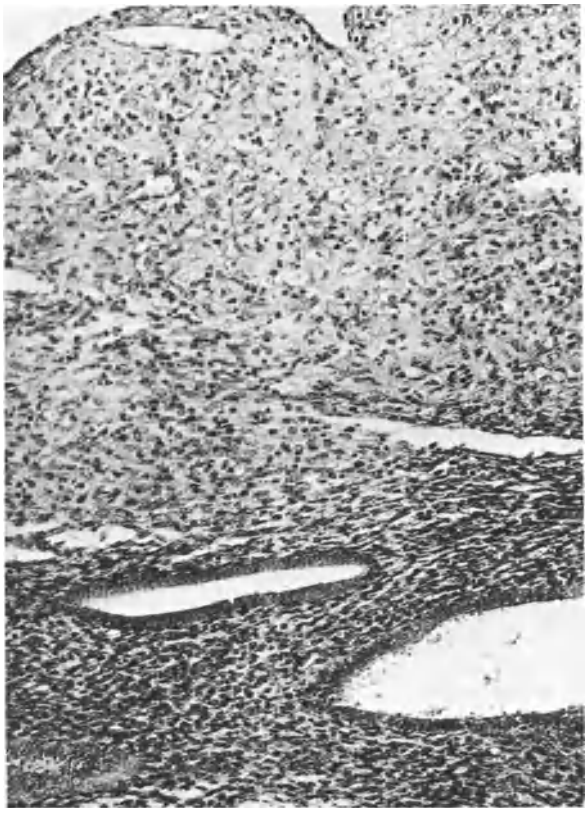


Fig. 122c. Legend see page 249

blastocyst. Another reason for their contraceptive effect might be a local hormonal dysfunction secondary to the inflammation they induce. Alterations in tubal transport, mechanical interference with implantation, local chemotactic effects on the endometrium or a focal release of cytotoxic products formed by the surface interaction with the endometrium have also been suggested as the mechanisms preventing conception (DAVIS and LESINSKI, 1970). In addition, macrophages induced by the inflammatory reaction may phagocytize spermatozoa or ova (DAVIS, 1972; see also previous literature cited there).

Because the mechanically-induced decidua develops only focally, it is easy to understand why pregnancy can occur when no inflammation is provoked. Pregnancy rates published for the LIPPES loop vary from 1.5% (LIPPES and ZIELEZNY, 1975) to 10% (LAST, 1974); for the DALCON shield from 1.3% (OSTERGARD, 1974) to 5% (HASPELS, 1973) and even 10% (PERLMUTTER, 1974). The rates, however, fluctuate considerably between countries (Costa Rica: 8.4%, Guatemala: 2%, according to SANNUEZA, 1975) and between investigative centers (SNOWDEN and WILLIAMS, 1975). Further complications caused by the mechanical intrauterine devices are pelvic inflammatory disease (TAYLOR *et al.*, 1975;

DAWOOD and BIRNBAUM, 1975; MEAN *et al.*, 1976; BÖHM *et al.*, 1977) with or without perforation of the uterus. Most perforations occurred when the device was inserted less than 8 weeks post partum (DAVIS, 1972). Pelvic actinomycosis, observed particularly with the DALCON shield (LOMAX *et al.*, 1976) produces irreparable disease in the pelvis and therefore is especially feared. Owing to its shape, the DALCON shield favors the growth of bacteria on its surface (WAGNER *et al.*, 1976) and its pinnated tail promotes the ascent of bacteria into the uterine cavity. Because it was associated with an excessive rate of septic abortions, it was withdrawn from the market in 1974 (TATUM, 1977).

The recently introduced **mediated intrauterine contraceptive devices** (JOHANNISSON, 1973; further literature see there) consist of a T- or 7-shaped strand of polyethylene, either impregnated with progesterone, which is slowly released, or wrapped with a fine copper wire. With this third generation of intrauterine devices, the harmful mechanical action is mitigated with a local hormonal (DOYLE and CLEWE, 1968; SCOMMEGNA *et al.*, 1970; 1974) or chemical action (ZIPPER *et al.*, 1968).

The *progesterone-medicated T-shaped devices* carry in their main vertical stem a depot which gives off about 65 µg of progesterone into the uterine cavity each day. That acts locally in a paracrine manner to induce perifocal decidualization and glandular atrophy of the superficial endometrium. The changes produced resemble an arrested secretion, and are sharply demarcated from the underlying functionalis, which proliferates or secretes normally, appropriate to the phase (Fig. 122b, c; DALLENBACH-HELLWEG, 1975). If the patients had taken oral contraceptive agents before the intrauterine device was inserted, then the lower layers of the endometrium disclose a correspondent deficient maturation. Measurements of the DNA in the nuclei of glandular epithelial cells of the focal arrested secretion gave low values like those obtained after administering gestagens systemically (JOHANNISSON *et al.*, 1977). Biochemical measurements, however, revealed no deviations in hormone levels as compared with normal control patients without intrauterine devices; they also revealed no influence on the hypothalamic-hypophyseal centers or ovarian function (TILLSON *et al.*, 1975; WAN *et al.*, 1977). Thus, when the gestagen is placed into the uterine cavity, it affects only the tissues in the immediate vicinity.

The perifocal arrested secretion induced by gestagen devices is characteristic in two chief respects. First, it is focal whereas the arrested secretion induced by administering gestagens either orally or parenterally involves the entire endometrium. Second, its glands are atrophied, whereas those of a decidualization brought about by the trauma of a purely mechanical device are normal. It is therefore possible in most cases to decide what type of device had been used (see Table 20). The contraception obtained is as good as that with systemically administered gestagens, giving a PEARL-index below 1%, since the implantation of the blastocyst depends on the qualities of the upper functionalis. An important difference, especially for the endometrium, is that the basalis and basal functionalis remain uninvolved and are spared for the next regeneration. As compared with a simple mechanical device, the assurance for contraception is increased because of the glandular atrophy induced. At the same time, the hazards of a generalized gestagen effect are avoided.

In contrast with those after mechanical devices, the number of complications arising is very small. The pregnancy rate is less than 1% (PHARISS *et al.*, 1974; WAL *et al.*, 1977). Inflammation of the endometrium rarely occurs since the decidua protects against it. The troublesome interval bleedings that at times develop (ZADOR *et al.*, 1976) may be explained by the focal and variable release of relaxin from aggregates of granulocytes, analogous to the break-through bleeding associated with diffuse arrested secretion (see p. 231). The sinusoidal vessels concentrated in these regions facilitate and intensify those small break-through hemorrhages (see also SHAW *et al.*, 1979). In addition ANCLA *et al.* (1967) described microthrombi in the vessels near the surface and HOHMANN *et al.* (1977) reported on defects of vascular walls associated with degenerating endothelial cells.

The *devices entwined with a copper wire* from 0.2 to 0.25 mm thick (T-, 7- and Multi-load) give off copper ions from their surface of 200 mm^2 into the intrauterine milieu. These like progesterone are absorbed by the superficial layers of the endometrium and have been reported in the secretory vacuoles of the glandular epithelium (SALAVERRY *et al.*, 1973). In contrast, electron-microscopic studies have failed to demonstrate the binding of copper ions to cell organelles, which might be related to their very rapid excretion (GONZALEZ-ANGULO and AZNAR-RAMOS, 1976).

Biochemical measurements indicated that the concentrations of copper and protein in the endometrium increase and those of zinc and manganese decrease (HAGENFELDT, 1972; HERNANDEZ *et al.*, 1975). These results suggest that copper exerts a metabolic effect on the endometrial cells. LARSSON *et al.* (1974) found the fibrinolytic activity increased. The concentrations of DNA and RNA remain unchanged, but the activity of lactic dehydrogenase of the superficial endometrium is depressed (WILSON, 1977). From the increase in the activity of acid phosphatase during the proliferative phase and the fall in the activities of alkaline phosphatase and β-Glucuronidase during the secretory phase, one may conclude that glycogen metabolism is affected (ROSADO *et al.*, 1976). Ultrastructural evidence of a disturbed catabolism of glycogen supported that conclusion (NILSSON *et al.*, 1974). The values for the biochemical measurements, however, vary among the different authors (cf. e.g., MERCADO *et al.*, 1972).

In contrast to the results of those biochemical analyses, light microscopic studies with routine and special stains failed to provide morphological evidence that copper had an effect on the endometrium (DALLENBACH, 1977; DALLENBACH-HELLWEG *et al.*, 1979). If prior hormonal therapy or functional disturbances are excluded, the endometria are appropriately developed, the surface epithelium is almost always intact, even where the copper wires have pressed against and indented the surface (Fig. 123). The aggregates of polymorphonuclear leukocytes in the glandular lumina or under the superficial epithelium undoubtedly come from the uterine cavity. We should not regard them as harbingers of inflammation, since the glandular epithelium is uninjured and intact. True inflammatory infiltrates appear only when endometrial function is deficient; that is, when its development is delayed or abnormal, so that atrophy and functional insufficiency lead to reduced resistance (DALLENBACH-HELLWEG, 1980). Usually in such cases the use of oral contraceptives has preceded the insertion of the intrauterine device.

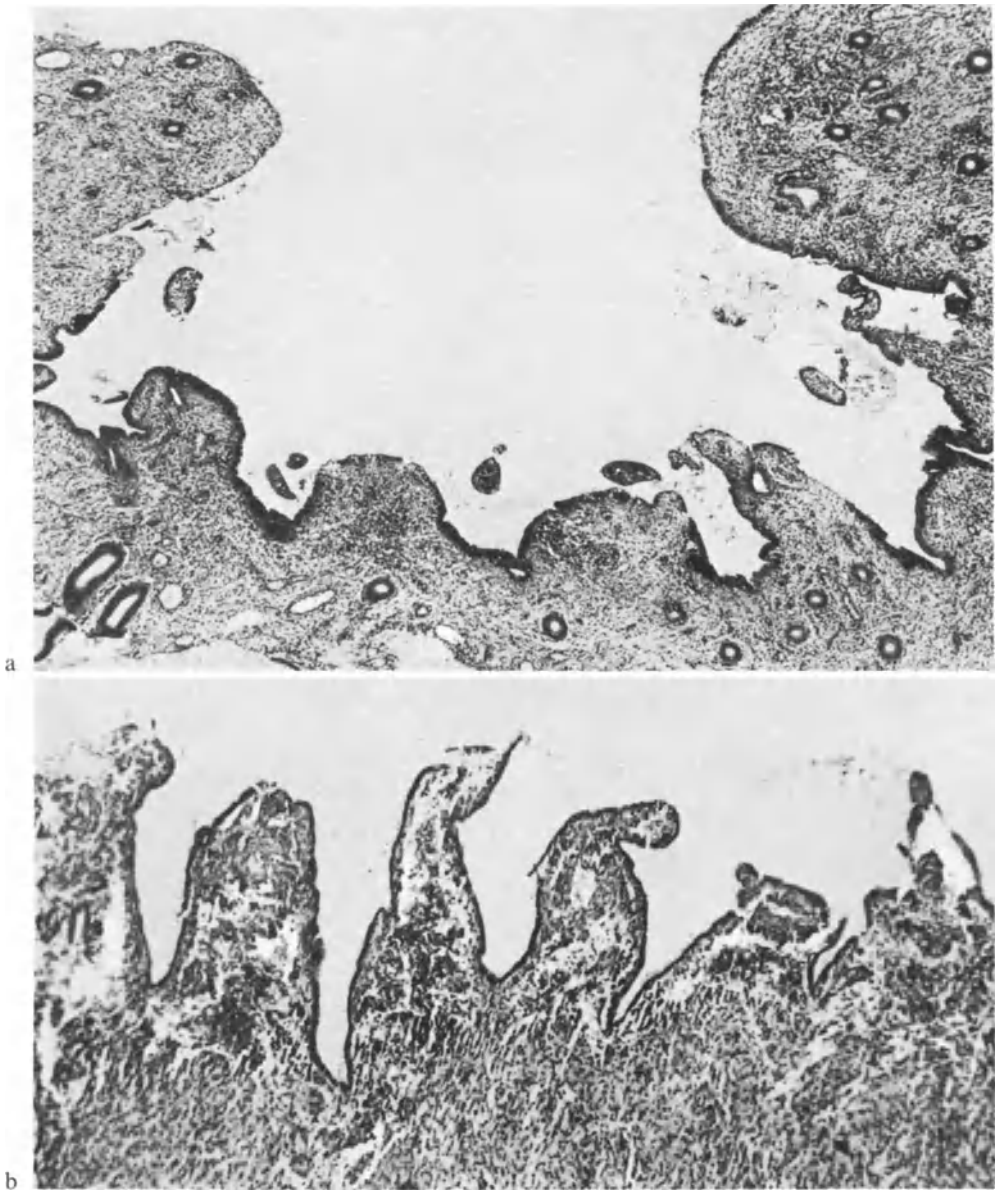


Fig. 123a and b. Corrugated surface of the endometrium produced by copper coils of intrauterine device. (a) T-form with wire 0.25 mm thick. (b) 7-form with wire 0.20 mm thick.

The contraceptive action of the copper-bearing intrauterine device, therefore, is best explained by the biochemically detectable changes it produces in the intrauterine milieu (OSTER and SALGO, 1975). We should also consider its possible effects on sperm (HICKS and ROSADO, 1976).

The pregnancy rates published for large patient-collectives vary between 1% and 2% (ORLANS, 1974; AKINLA *et al.*, 1975; JAIN, 1975; PIZARRO *et al.*, 1977), or even under 1% (TATUM, 1973; LIEDHOLM and SJÖBERG, 1974). The complication rate is comparably low. The rare perforations with the copper-T or 7-device occur typically through the endocervix (CEDERQVIST and FUCHS, 1974; NYGREN and JOHANNSEN, 1974).

The number of extrauterine pregnancies occurring with all types of intrauterine devices is clearly increased (LEHFELDT *et al.*, 1970; TATUM, 1976; ERKKOLA and LIUKKO, 1977; TATUM, 1977; ZIELSKE *et al.*, 1977). The reasons given for that are: the intrauterine device acts only locally in the uterine cavity; it also promotes infections of the fallopian tube. Rare reports of ovarian pregnancies continue to appear (PANE *et al.*, 1970; PUGH *et al.*, 1973).

That fertility was not affected after removal of an IUD was observed in two large series of patients (HATA *et al.*, 1969; WAJNTRAUB, 1970). Conception may be slightly retarded, but the length of use of the intrauterine contraceptive device made no difference. After 18 months, 93.1 per cent of the patients had conceived.

c) After Intrauterine Instillation

Intrauterine instillation may be performed for two reasons; first, for hysterosalpingography: the procedure involves injecting a contrast medium of radiopaque oil (e.g., Lipiodol). Second, a liquid tissue adhesive may be instilled into the uterine cavity and into the lumina of the fallopian tubes to control persistent menorrhagia and to cause permanent sterilization. For that purpose, formaldehyde, hot waxes or cyanoacrylates have been used. STEVENSON and TAYLOR (1972) injected methyl-2-cyanoacrylate into twelve patients between day one and sixteen weeks before hysterectomy. The liquid polymerized on the endometrium within about twenty seconds after the intracervical injection. It produced inflammation, necrosis and complete stripping of the superficial endometrial layers. With a high secretory endometrium the basal layers were preserved for later regeneration. With a low proliferative endometrium, the inflammation involved the basal layers as well, making regeneration impossible. A granulation tissue with multinucleated giant cells developed in some regions, whereas other portions usually showed stromal fibrosis with complete loss of glands.

Various histological changes may occur, depending upon the type of substance used for instillation, upon the individual reaction to it, upon the height of the endometrium, and upon the time that elapses between instillation and examination of the endometrium. Occasionally one may come across a peculiar histiocytic or granulomatous reaction with or without traces of foreign material in glandular lumina or in the endometrial stroma. The etiology of that reaction may be perplexing (see Fig. 124). In such instances, a previous intrauterine instillation (perhaps decades before) can only be suspected, since generally it is impossible to obtain a correct clinical history. We make our presumptive diagnosis only after excluding a systemic granulomatous disease (tuberculosis, sarcoidosis etc.) and by comparing the changes we see with similar lesions known to be produced by instillation.

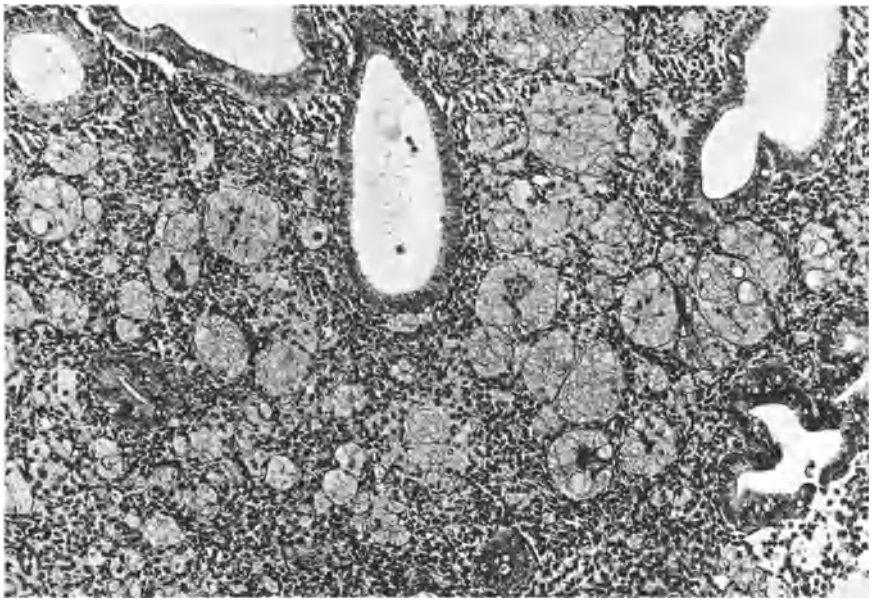


Fig. 124. Histiocytic storage disease. In the stroma of the functionalis between normal appearing glands there are countless large and small clusters of histiocytic cells ladened with an unidentified foamy substance. The excessive accumulation of the foamy substance has displaced the nuclei of the histiocytes

d) Regeneration after Curettage

If the endometrium is curetted during a phase of the cycle not followed by menstrual bleeding, then the mucosa that regenerates is without the hormonal stimulus normally acting during the postmenstrual proliferative phase. The question often asked—does a new cycle begin after a curettage or does the old continue according to plan—can be answered only in part. Studies of the effects of curettage in large groups of women with regular cycles disclosed that 82.6 per cent menstruated at the expected time. In 7.2 per cent the cycle was shortened, and in 10.2 per cent it was prolonged (JÖRGENSEN and ENEVOLDSEN, 1963). MCLENNAN (1969) found that regeneration after curettage was primarily delayed during the secretory phase, whereas during the proliferative phase or during a hyperplasia the endometrium promptly regenerated. In no instances did the cycle fluctuate more than a few days. From these results we may infer that the trauma of a curettage does not disturb the hormonal cycle of the ovary. If, however, a hormonal dysfunction existed beforehand, then a curettage may greatly prolong the cycle.

As histological studies indicate, the raw surface left after curettage regenerates very slowly, often remaining deficient since the processes of healing proceed independently, usually out-of-phase with the secretion of the ovarian hormones. A complete curettage may not be so complete as intended, as a hysterectomy specimen removed shortly after curettage may often show, with portions of endometrium remaining in the fundus or tubal recesses. These remnants will continue

to undergo the regular changes of the cycle, which however may proceed faster than normal, being stimulated by the trauma. Thus, by the twentieth day the stroma in these parts may show a predecidual or decidual change like that incited by an intrauterine device. Even a strip-biopsy may cause the secretory phase to accelerate or, because of the mechanical stimulus, induce a spontaneous ovulation at the end of an anovulatory cycle. NOYES *et al.* (1950) reported that in two-thirds of their patients the first menstruation after curettage began a few days earlier than expected. The subsequent menstruations, however, occurred at the proper times.

A curettage performed with too much zeal, particularly when repeated several times or done after abortion or pregnancy, may result in so much basalis being removed that *intrauterine adhesions* (synechiae) develop *as a late complication.* According to several authors (ASHERMAN, 1948; FOIX *et al.*, 1966, see also for further literature; TURUNEN, 1966) these adhesions, formed after total loss of the endometrium, not infrequently cause a secondary obstructive-type amenorrhea and sterility (ASHERMAN's Syndrome). Usually they are diagnosed by hysterography (SIEGLER, 1962; TOPKINS, 1962; HALBRECHT, 1965; DMOWSKI and GREENBLATT, 1969), seldom in the extirpated uterus, apparently because they are easily overlooked. As to be expected, if such a uterus is curettaged, few if any curettings may be obtained and these will chiefly consist of scar tissue and fragments of myometrium. The endometrial cavity may not be obliterated but instead crisscrossed by threadlike synechiae composed of endometrium, fibrous tissue or smooth muscle. The bands of endometrial tissue often undergo the same cyclic changes as the remaining endometrium or equivalent parts of the basalis. Usually by the time synechiae have formed the inflammatory changes have disappeared (FOIX *et al.*, 1966). Adhesions that produce stenosis or occlusion only at the isthmus or in the endocervical canal may cause false amenorrhea with hematometra. If the patient remains fertile and becomes pregnant, then the likelihood the pregnancy will end with an abortion, miscarriage, placenta accreta or a pathological presentation of the fetus are great (JEWELEWICZ *et al.*, 1976).

Besides an overly ambitious curettage, other causes for such endometrial adhesions are the less common necrotizing endometritis (after criminal abortion with soap solutions) or caseating tuberculous endometritis.

When the endometrium is totally destroyed, including the basalis, replacement by endometrial transplantation may prove beneficial. A few investigators have reported successful pregnancy following transplantations (REIFFENSTUHL and KROEMER, 1965; TURUNEN, 1966, see also for further literature).

Endometrial cryosurgery, a fairly new method and seldom used even today for the control of dysfunctional bleeding or for sterilization, produces extensive necrosis of the endometrium. Such necrosis may occasionally involve the myometrium, leading to the formation of an abscess (BURKE *et al.*, 1973). The endometrium may regenerate focally if portions of the basal layer had been preserved. More experience with this method is needed before we can decide whether it is practicable.

D. The Diagnosis of Pregnancy from Curettings

1. The Early Intrauterine Pregnancy and Its Disturbances

a) Therapeutic Abortion (induced abortion)

If for clinical or socioeconomic reasons it becomes necessary to interrupt an early pregnancy, a curettage usually yields so much amnion, immature placenta, and abundant decidual tissue that no difficulties in diagnosis arise. Although these tissues generally are normal, they are of value for us, serving as ideal standards which we need for comparison in evaluating and diagnosing tissues from diseased pregnancies. Histological, cytological and cytogenetic studies of the embryo lie within the province of research workers who ordinarily concern themselves with specific problems, for example, chromosomal abnormalities, inherited deficiencies of cellular enzymes. Then too, study of the embryo in the daily routine of gynecological pathology is seldom required, since a primary injury of the fetus causing abortion almost always reveals itself by failure of the fetal vessels in the placental villi to develop.

By using the well-known stages of development of placental villi as our guidelines, we can determine with fair accuracy the age of gestation of a therapeutic abortion merely by examining the *placental tissue*. On the thirteenth day of gestation the primary villi begin to form from the syncytium, which developed from the cytotrophoblasts[4] after these came in contact with maternal blood on the ninth day. From the fifteenth day on fetal mesoderm begins to penetrate the solid, primary villi, converting them into the secondary villi. On about the twentieth day capillaries sprout forth in the mesodermal cores, forming the tertiary villi (Fig. 125). The initial erythrocytes in these vessels are nucleated, but by

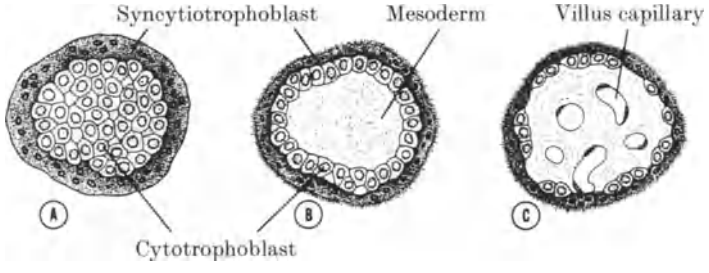


Fig. 125. Normal stages in the development of placental villi, as seen in cross-section. (A) primary, (B) secondary, (C) tertiary villus

[4] In accord with modern usage we refer to the cells of the inner layer of the trophoblast as "cytotrophoblasts" or "cytotrophoblastic cells", and those of the outer syncytial layer as the "syncytiotrophoblasts" ("syncytiotrophoblastic cells"), acknowledging however as HERTIG does (1968), that the term "trophoblasts" is often misused.

the onset of the second month of pregnancy only anuclear erythrocytes are normally seen. From the stage of the secondary villi on, two distinct layers of trophoblasts envelope the villi. With progressive differentiation, however, the inner layer of cytotrophoblasts gradually regresses, leaving the outer layer of syncytiotrophoblasts broader and thus more conspicuous. By the end of pregnancy only a few scattered cytotrophoblasts remain. Also, the layer of syncytiotrophoblasts becomes thinner with time. The villous stroma about the blood vessels diminishes as these enlarge and dilate. In that way the distance separating fetal and maternal blood becomes less and less, adapting to the growing nutritional demands of the embryo. In addition, through growth and subdivision into finer branchings the surface area of the villi is greatly increased. The Hofbauer cells found in moderate numbers in early pregnancy gradually disappear as pregnancy advances. It is not unusual to find, even in what is regarded as a normal early pregnancy, that a few villi have undergone hydropic degeneration. They are seen in about twenty per cent of therapeutic abortions (JURKOVIC and MUZELAK, 1970), most commonly in the chorion laeve (FUJIKURA *et al.*, 1971). On the other hand, a therapeutic abortion may be induced before abnormal products of conception are expulsed spontaneously. Consequently, a small percentage (3%–6%) of therapeutic abortions show abnormalities in placental-fetal development.

The *decidua* first begins to develop a few days after implantation. The histological changes that distinguish the predecidual stage from the decidual stage, however, begin to manifest themselves by the ninth day after ovulation (that is, two days after implantation). The decidual cells continue to increase in size; their pale nuclei with prominent nucleoli enlarge, thereby increasing their surface area. Other decidual cells accomplish the same by developing double nuclei. The abundant cytoplasm of the decidual cells denotes increased amounts of RNA, glycogen, and various enzymes, particularly carbonic anhydrase and 3β-steroid dehydrogenase, which indicates the decidual cells actively participate in the metabolism of steroids. Correlating with that is the increase in the smooth endoplasmic reticulum, a change that reaches its maximum at about the fortieth day of gestation. The endoplasmic reticulum is sparsely granular; its differentiation is maximal by the fortieth day of pregnancy. The margins of the cells are now sharp and distinct, enveloped by fine reticular fibers. Contacts or gap-like junctions join processes that sprout from the same cell (LAWN *et al.*, 1971). As the decidual change progresses, the cells come closer together, establishing contacts with one another and an epithelioid arrangement, actively adapting to the demands imposed by the rapidly growing placenta and fetus (LIEBIG and STEGNER, 1977). Ultrastructurally, the metabolic activity of the decidual cells appears to be maximal by the seventieth day of pregnancy and begins to decline after the hundreth day (WYNN, 1974). The number of endometrial granulocytes has by then greatly increased. Their nuclei become lobulated, enlarging their surface area. Their intracytoplasmic granules increase in size and number. The glands, which start to produce glycogen again, remain highly active until the eighth week of gestation. Thereafter they begin to involute. A most striking change is the abundance of dilated, thin-walled vessels in the stroma, some of which reveal the typical endothelial proliferations induced

by relaxin. The high fibrinolytic activity found at the time of implantation decreases; instead, the ground substances of the decidua become rich in acid mucopolysaccharides (SCHMIDT-MATTHIESEN, 1968; see also p. 35). The dense extracellular material surrounding the mature human decidual cell ultrastructurally resembles the basement membrane of the epithelium (WYNN, 1974).

By the seventeenth day of gestation the decidua has reached its greatest height, measuring about one centimeter. Later when the decidua basalis, capsularis and parietalis separate, and because the blastocyst and placenta grow so rapidly, the destructive and remodeling processes that normally evolve in the decidua may be accompanied by small necroses and focal infiltrates of polymorphonuclear leukocytes. Localized aggregates of endometrial granulocytes with their lobulated nuclei should not be mistaken however for inflammatory cells. It is relatively easy to differentiate the two kinds of cells, not only by using special stains but also by showing that where leukocytes are aggregated the tissue is undergoing necrosis and lysis. Where intact endometrial granulocytes congregate, one never finds such destruction of tissue. It is important to realize that small resorptive necroses normally occur in healthy pregnancies (therapeutic abortions). Accordingly, a diagnosis of septic abortion should be made only when extensive inflammation and necrosis are found.

b) Spontaneous Abortion and Criminal Abortion

Attempts to compare the frequency of spontaneous abortion with that of criminal abortion are fraught with immediate failure. The very clandestine nature of criminal abortion precludes any gathering of data about it. On the other hand, the functional or morphological anomalies that cause spontaneous abortion may escape histological search. If malformations are detected, they may prove important in evaluating the prognoses of future pregnancies for the patient. Contrary to earlier opinions, one can find recognizable remnants of chorionic villi in curettings from 75 per cent of the women suffering spontaneous abortion (THOMSEN, 1955). All "blighted" or abortive ova disclose disturbances in the development not only of the embryonic anlage but also of the chorionic villi, particularly their differentiation into tertiary villi at the proper time. THOMSEN (1955) was able to demonstrate such disturbed development in 61 per cent of all spontaneous abortions, but only in 3 per cent of proven criminal abortions. These statistics should encourage every pathologist to look for possible abnormalities, especially in the placenta, in every specimen of abortion submitted.

Factors acting during the first trimester to cause abortion of the conceptus may be endogenous (genetic) or exogenous (maternal). Since the abortions occurring during the second trimester are often caused by placental disturbances (for example, circumvallate), they are outside the domain of this monograph and I shall not discuss them further.

HERTIG and SHELDON (1943) and HERTIG and LIVINGSTONE (1944) estimated from a large series of patients in Boston that 25 per cent of all pregnancies ended with abortion; of this 25 per cent, about a half occurred spontaneously. In turn, about 62 per cent of that half (from 30–70 per cent according to other authors) was due to **"blighted" or pathologic ova** (with early death or absence

of the embryo, hypoplasia of the trophoblasts, hydropic change or fibrosis of the chorionic villi); 38 per cent was due to maternal factors (anomalies of the uterus, basal hematoma, or bacterial infections). About 4 per cent of all spontaneous abortions were habitual. In the majority of these the embryo was defective; repeated abortions by the same patient disclosed the same defect (WALL and HERTIG, 1948).

Spontaneous abortions resulting from "blighted" (pathologic) ova sharply increase in the older age-groups (MCMAHON *et al.*, 1954). That is particularly true for abortions with demonstrable *chromosomal anomalies* (KERR and RASHAD, 1966; also for earlier literature; GROPP, 1967; JACOBSON and BARTER, 1967). Chromosome anomalies arising from faulty gametogenesis or gene mutation are found in 27%–50% of all spontaneous abortions (BOWEN and LEE, 1969). They are particularly frequent in recurrent abortions (LUCAS *et al.*, 1972; ROTT *et al.*, 1972) and in virtually 50% of anatomically abnormal embryos and fetuses (SINGH and CARR, 1967); they occur in only 3.3 per cent of therapeutic abortions (LARSON and TITUS, 1970) and in 0.5 cent of live-born infants. According to newer studies (YAMAMOTO *et al.*, 1975, TSUJI and NAKANO, 1978), however, chromosomal abnormalities were identified in 6.8% of induced abortions. The trisomies increased as the mothers became older; the monosomies were age-independent. In abortions with abnormal chromosomes the period of gestation is significantly shorter and the embryonic development less advanced than in abortions with normal chromosomes (PHILIPPE and BOUE, 1969; MIKAMO, 1970). In most of the chromosomal anomalies described to date polyploid sets have been found. Such sets are commonly associated with missed abortions in which the chorionic villi reveal hydropic swelling. In ten such abortions, CARR (1969) was able to demonstrate triploidy in nine and tetraploidy in one. By using the method developed by BARR *et al.* for determining nuclear sex chromatin. BOHLE *et al.* (1957) and HIENZ and STOLL (1962) were able to show that during the third and fourth month of pregnancy the mortality of male fetuses exceeded that of the female fetuses. From comprehensive studies HERTIG (1967) concluded that 50 per cent of all ova fertilized after a delayed ovulation (on the fifteenth day of the cycle or later) aborted, whereas when ovulation took place before the fourteenth day, then 92.3 per cent of the fertilized ova developed normally. Delayed ovulation induces intrafollicular overripeness of the ovum. That may lead to disturbances in both meiotic metaphases because of degeneration of spindle fibers and loss in the polarization of chromosomes (MIKAMO, 1970). According to new estimates, half of all fertilized ova die before they begin to implant because of chromosomal abnormalities (KNÖRR and KNÖRR-GÄRTNER, 1977).

Other generally exogenous causes of chromosomal damage and an ensuing hydatidiform mole are: *vitamin deficiencies, X-irradiation, hypoxemia* as well as *deficiency or overdosage of endogenous or exogenous sex hormones* (GROSSER, 1948; MEY, 1961). Recent observations by CARR (1970) support that idea. He compared 54 abortuses from women who conceived within 6 months after discontinuing hormonal contraception with 227 unselected abortions. Chromosomal anomalies were present in 48 per cent of the post-contraceptive group but were found only in 22 per cent of the unselected group. Thirty per cent of the abortuses of the post-contraceptive group revealed polyploidy as compared

with only 5 per cent of the control group. Ninety-five per cent of all blastocysts that implanted during use of chlormadinone proved to be malformed with hydropic, avascular villi and atrophic trophoblastic cells (KÜHNE *et al.*, 1972). Histological and embryological studies revealed that after stopping antifertility agents the frequency of disturbances of early embryogenesis doubles (POLAND, 1970). Our own studies support these statistics, and we found that the composition of the agent taken determined more the degree of damage than did the length of time since discontinuing the agent (DALLENBACH-HELLWEG, 1978). The contradictory results of other authors (BOUE *et al.*, 1975; LAURITSEN 1975; KLINGER *et al.*, 1976) no doubt depend upon the differences in composition of the antifertility agents used or upon the differences in the ages of the patients studied: for example, in the collective reported by LAURITSEN, after discontinuing the agents, young women developed chromosomal anomalies almost twice as often as the older women, although spontaneous anomalies are known to occur more often in the older. Other reports suggest that inducers of ovulation also increase chromosomal anomalies (BOUE and BOUE, 1973).

In addition, an abnormally developed endometrium may disturb implantation of the blastocyst, as for example, an irregularly proliferating endometrium or a deficient secretory endometrium. If the fertilized ovum implants improperly, such as in polypoid implantation, abortion may result (KRONE, 1961). Since blighted ova often are discarded shortly after fertilization and make no attempts to implant, they go unnoticed and are never registered as spontaneous abortions. For that reason disturbances of implantation assume a subordinate theme in this chapter and because of their signs and symptoms are classed and discussed under the causes of infertility. In contrast, secondary disturbances of implantation, such as bacterial infections, may cause abortions that are clinically recognized. GRUENEWALD (1965) suggested that a premature shedding of the decidua might cause abortion. Such a decidual detachment would be possible if too much or uninhibited relaxin were released from endometrial granulocytes. In our curettings of abortions after discontinuing oral contraceptives, we have found a deficient secretory phase in about 50 per cent of the specimens, and hydropic swelling of avascular chorionic villi with atrophy of the trophoblast about twice as often as in unselected abortions (see Fig. 126).

After LANGHANS (1901), HITSCHMANN (1904) also concerned himself with the **microscopic diagnosis** of abortion just before he undertook a study of the menstrual cycle. The detachment in abortion, unlike that of a normal menstruation or pregnancy, usually develops from necrosis in the upper layer of the decidua. The placenta and decidua almost always involute completely. The degree and extent of their involution are dependent on how long the initiating hemorrhage lasted and on the cause of the abortion. If the embryo dies first then involution is protracted, and therefore may assume extreme forms. With bacterial infections the decidua is particularly subject to rapid necrosis, thereafter the placenta. By carefully studying all structures it is often quite possible to conclude what the etiology of the abortion was.

The *glands* of the **decidua** may react in various ways, depending upon whether the embryo perished first, or secondarily after destruction (usually by infection) of the placenta. If the embryo dies first, the placenta may survive for long periods,

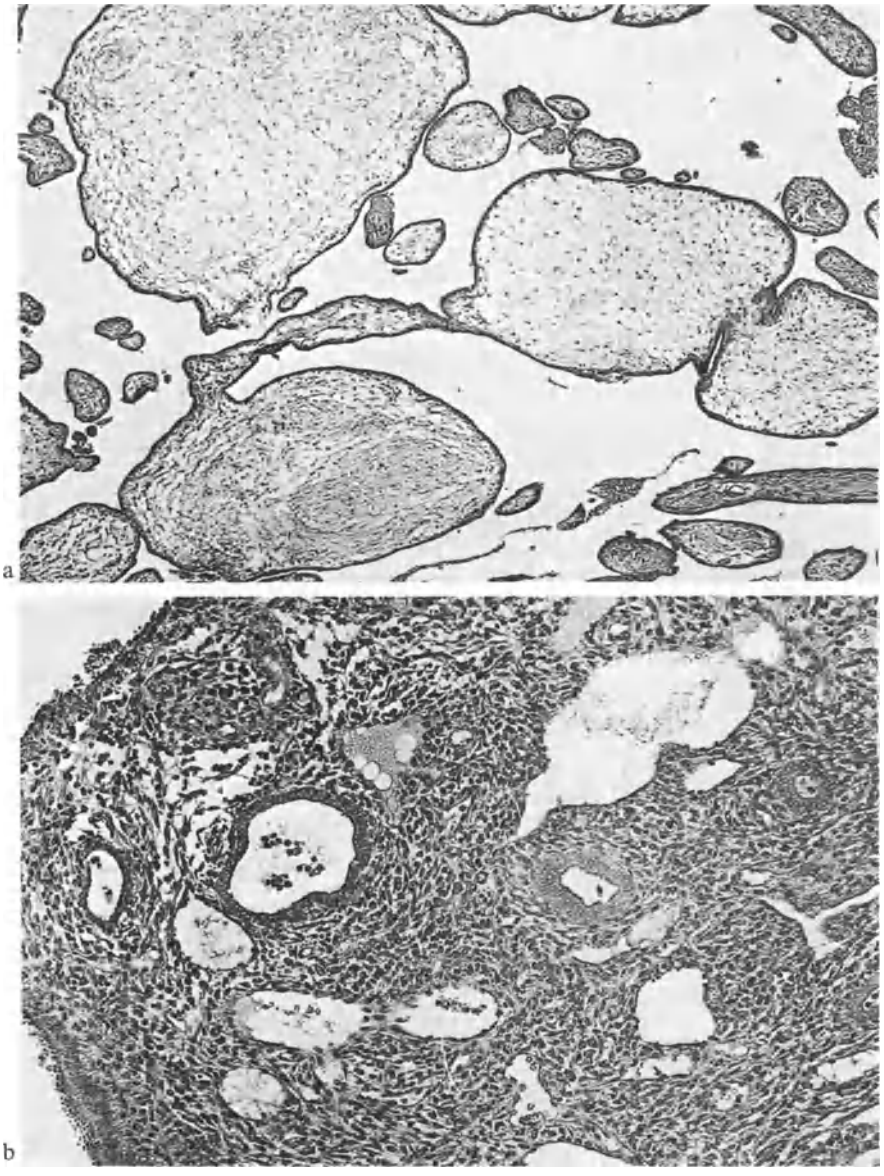


Fig. 126a and b. Spontaneous abortion at fourth month, after discontinuing oral contraceptives which had been taken continuously for six years. (a) Malformed avascular hydropic villi. (b) The associated endometrium irregularly and deficiently developed

producing its hormones, particularly gonadotropin, until it is discharged (CASSMER, 1959). Since the dead fetus is unable to properly assimilate and metabolize gonadotropin, the hormone accumulates in the maternal circulation and decidua (ZONDEK, 1947). In the decidua gonadotropin apparently overstimulates the glandular epithelial cells, causing their nuclei to enlarge, the chromatin to

greatly increase, and their cytoplasm to swell and become unusually clear (Fig. 127). This phenomenon, first mentioned by DEELMAN (1933), then by OVERBECK (1953), was more precisely described by ARIAS-STELLA in 1954. It can be produced in the female rat by injecting it with gonadotropin (ARIAS STELLA, 1955; DALLENBACH, 1966, see also for review of literature) or in women with clomiphene (BERNHARDT *et al.*, 1966). The phenomenon indicates a hormonal hyperstimulation, not an involution as some authors maintain. In animal experiments after the hormone is discontinued a few days the cellular changes disappear. Histochemical studies of the abundant, clear cytoplasm to date have revealed only PAS-positive granules in it (OVERBECK, 1959) which were susceptible to digestion by diastase (BESWICK and GREGORY, 1971). Electron-microscopic studies (DE BRUX and ANCLA, 1964; TRASHER and RICHART, 1972), however, suggest the glandular epithelial cells actively secrete and have a high protein metabolism. Microspectrophotometric measurements of their nuclear DNA always yields polyploid values but never aneuploid (SACHS, 1968; WAGNER and RICHART, 1968). The nuclei of some glandular epithelial cells, however, may be degenerated instead of hyperactive, indicating the phenomenon is waning. Occasionally we see signs of hyperactivity and involution together, a reason perhaps why opinions about the cause diverge (FIENBERG and LLOYD, 1974). If one examines the histological preparations carefully enough, one can find an Arias-Stella phenomenon in about 50 per cent of all abortions (and possibly the cause of the abortion as well). If an Arias-Stella phenomenon is lacking, then the decidual and endometrial glands are often collapsed, having prominent star-like shapes similar to those of irregular shedding (see Fig. 71), which at times may also be caused by death of the fetus and placental tissues. In these instances we assume both die at the same time, and all hormones of pregnancy rapidly decrease.

If no bacterial infection occurs to provoke an intense infiltration of inflammatory cells, then the *decidual cells* always involute very slowly. They gradually shrink, their cell-margins pulling away from one another to leave wide spaces between them. A well-developed network of collagenous fibers or vast "lakes" of homogenous protein-rich matrix are left behind. The cytoplasm of the decidual cells becomes homogeneous, staining intensely. The nucleus condenses, appearing pyknotic. As a characteristic feature of their slow involution, the decidual cells form in their cytoplasm socalled "collagen inclusions" (HAMPERL, 1958), which become visible only with stains for connective tissue (Fig. 128; Color Plate IIc). As electron-microscopic studies have proved, however, these are not true inclusions but rather deep indentures of the cell membrane filled with pericellular fibrils of collagen (WESSEL, 1959). They represent a disturbance of collagen formation at the cell membrane, and are associated with the shrinkage of the cell and its loss of turgor (DALLENBACH-HELLWEG, 1961). Thus, we find them most commonly in decidua of blighted ova as well as in the intrauterine decidua of extrauterine pregnancies (see p. 282). At times these "collagen inclusions" may be the only diagnostic clue that an abortion had occurred a while before.

In contrast, with intense inflammation the decidual cells, until then intact, undergo rapid necrosis and enzymatic lysis; the network of connective tissue disintegrates, and the reticulum fibers dissolve away (Fig. 129). Occasionally one finds portions of necrotic decidua adjoining portions that are in the process

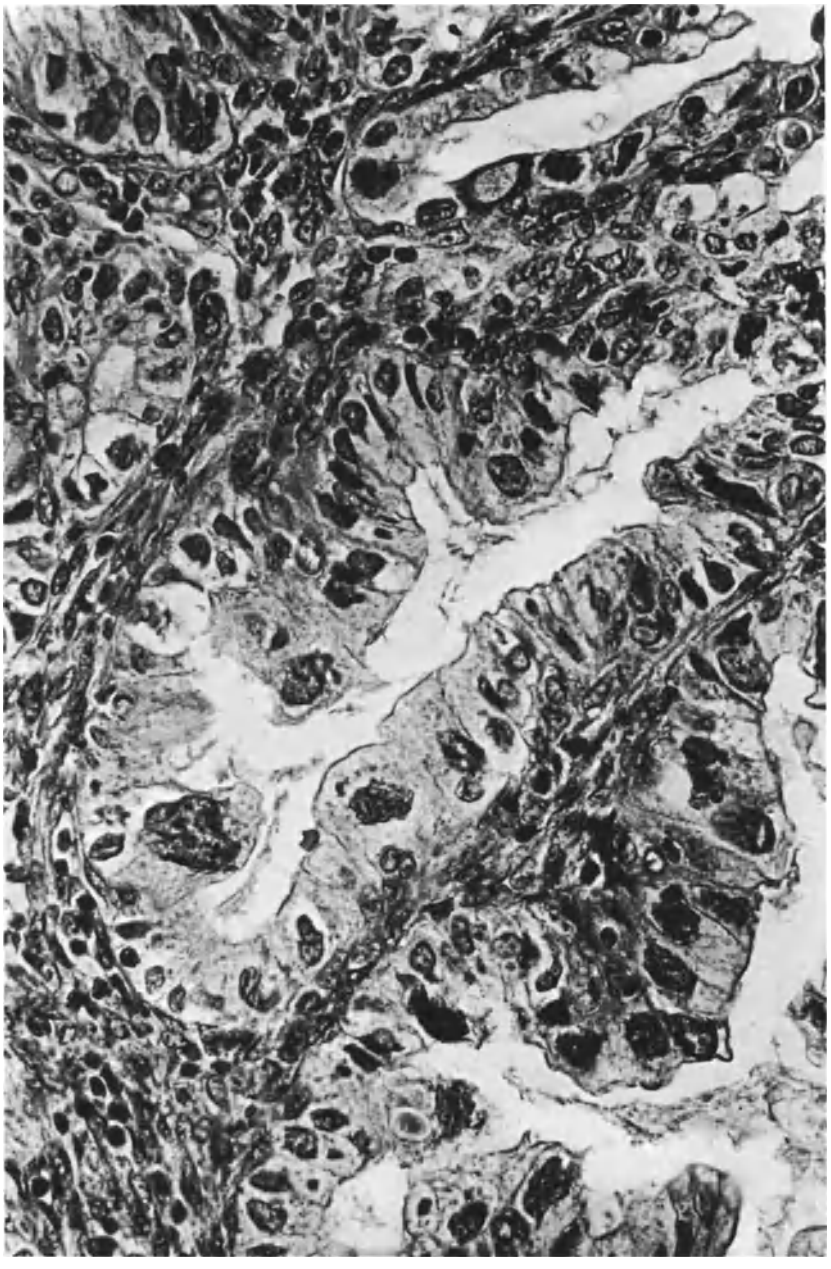


Fig. 127. Arias-Stella-phenomenon after intrauterine abortion

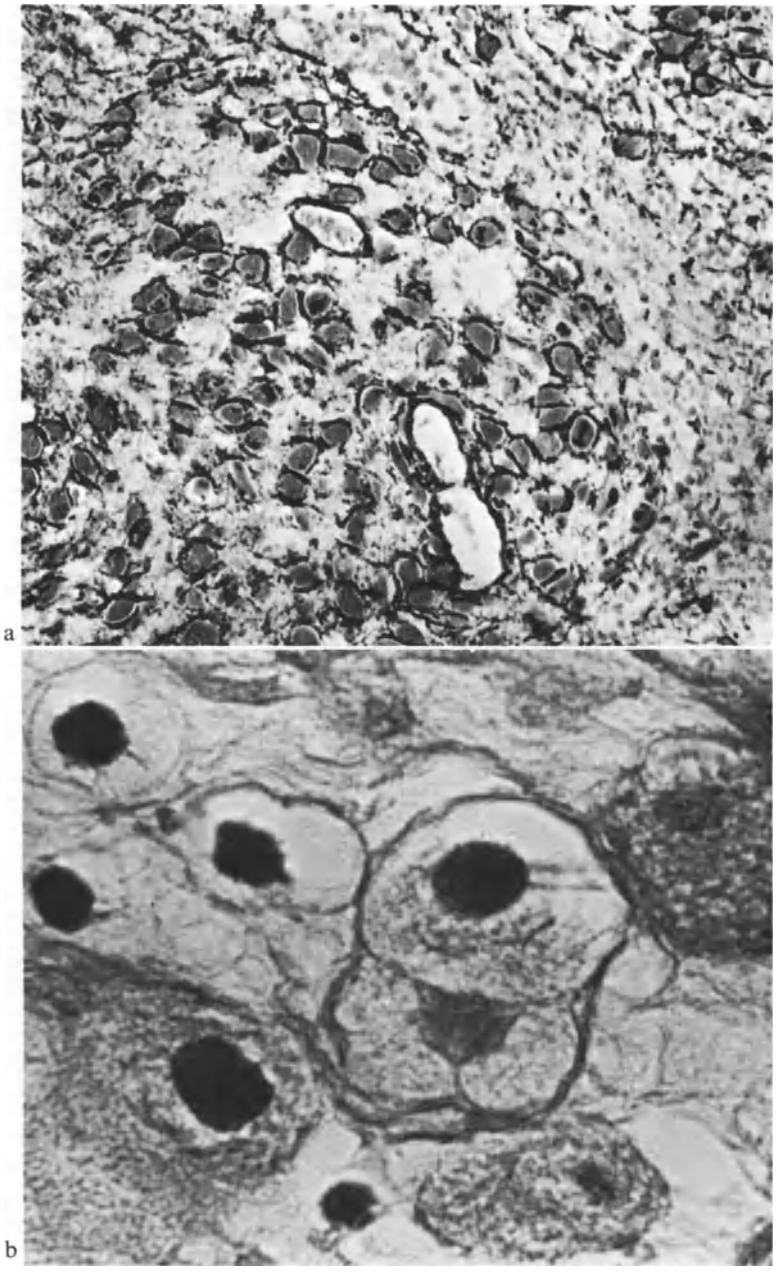


Fig. 128 a and b. Collagen inclusions in slowly regressing decidual cells. (a) Silver impregnation after GOMORI: The reticular fibers surrounding the decidual cells are thickened. The inclusions in the cells are black. (b) Masson trichrome stain. Plume-shaped inclusion in the lower part of the middle cell

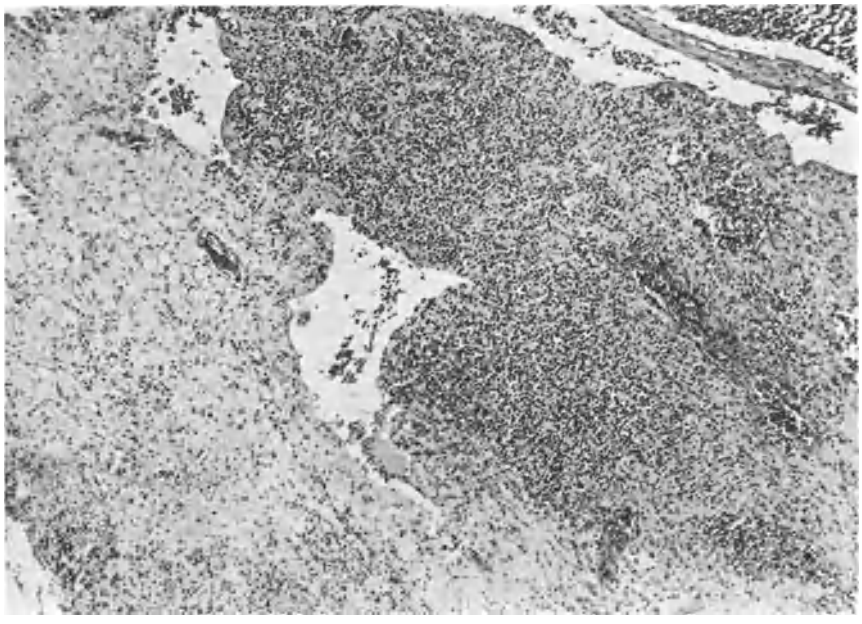


Fig. 129. Focal necrosis of the decidua (at the right) with heavy infiltrates of polymorphonuclear leukocytes

of slowly shrinking, usually when the decidual remnants become secondarily infected long after the fetus has died (*Endometritis post abortum*). The inflammations causing an early abortion usually are non-specific, with a few exceptions such as listeriosis, mycoplasma, or viruses (see p. 156). Specific infections generally lead to stillbirth in the third trimester. In 34 women with repeated abortions, RAPPAPORT *et al.* (1960) were able to culture listeria from the cervical secretion in 25. CRAMER and WADULLA (1950) recovered leptospira in a few abortions. In addition, toxoplasmosis appears to be a rare cause for abortion (SHARF *et al.*, 1973; see also p. 156). In rapid involution as well as in slow, protracted involution the widely dilated, thin-walled *vessels* of the decidua usually are filled with blood. Occasionally one finds pronounced endothelial proliferation (Fig. 130).

If the portions of decidua come from regions where chorion has invaded (decidua basalis), then one will find *trophoblasts* with one or more nuclei. These cells also involute but in general survive longer than the surrounding decidual cells. When no placental tissue is found in the histologic sections, then the discovery of such trophoblasts amid remnants of decidua may be decisive in differentiating an intrauterine pregnancy from an extrauterine (Fig. 131).

The **placental villi** found in the curettings of induced abortions or of spontaneous abortions due to maternal causes usually are regular in shape and well-preserved, although the decidua is shrunken or necrotic. Occasionally, however, the villi are necrotic or hyalinized. In these instances they lose their sheath of trophoblastic cells, and are embedded in coagulated blood or fibrin. Only with the aid of connective-tissue stains (for example, van Gieson; Fig. 132) can they be distinguished from the "sea" of fibrin that engulfs them ("ghost villi").

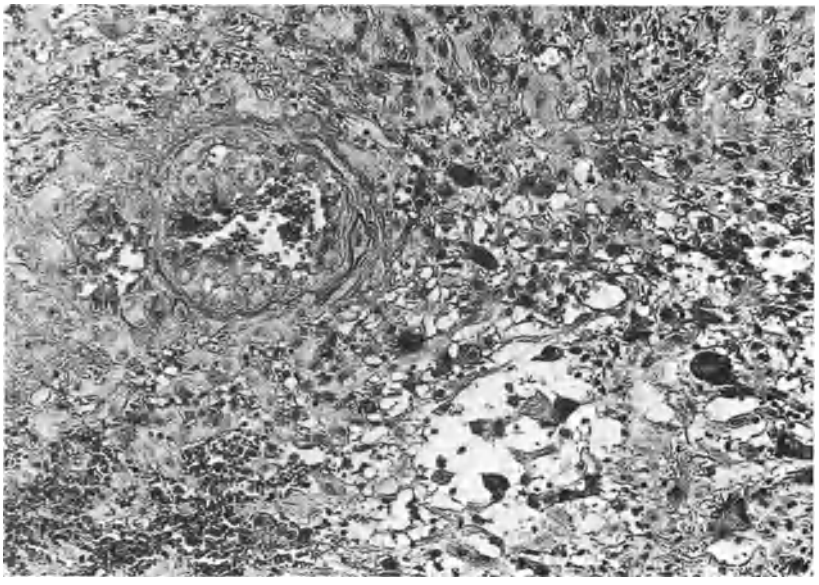


Fig. 130. Chorionic invasion of trophoblastic cells into the decidua. Endothelial cells lining maternal arteriole are proliferating. Note the differences between the two types of cells

Between these two extremes one often finds all transitions of rapid or gradual degeneration of villi. One must take care in differentiating the *regressive changes of normally structured villi* from those of villi primarily maldeveloped. Such a distinction is possible, however, only if the villi are not necrotic and are present in sufficient numbers, since occasionally even when development proceeds regularly a few villi may appear abnormal. If after normal development the maternal circulation fails, then the trophoblastic syncytium degenerates first. If on the other hand the fetal circulation fails, then the regressive changes first appear in the blood vessels and stroma of the villi; nonetheless, these structures remain recognizable as such until complete necrosis sets in.

Primary malformation of the villi is characterized by definite changes, which vary in their severity depending upon the age of the pregnancy (or length of survival of the placenta). If the villi fail to become vascularized through defective growth or death of the embryo, they do not degenerate but instead develop abnormally. Earlier or later, the villi swell through hydropic change, ultimately reaching sizes much greater than normal. As HERTIG (1968) emphasizes, the swelling is not a true degeneration but rather the result of the immature trophoblast continuing to take up fluid. By necessity, the fluid accumulates in the loose stroma of the villi since these lack blood vessels for carrying the fluid away. (VOGEL, 1969, believes a "mole-like degeneration" of the villi represents a special form of secondary alteration in embryonal abortion.) Usually as the villi swell the trophoblasts covering them become atrophic, the nuclei of the syncytiotrophoblasts pyknotic. Langhans cells always are absent (Fig. 133). Such changes develop very rarely in villi of normal structure (ABACI and ATERMAN, 1968; NAYAK, 1968). The hydropic villi of blighted ova histologically differ from

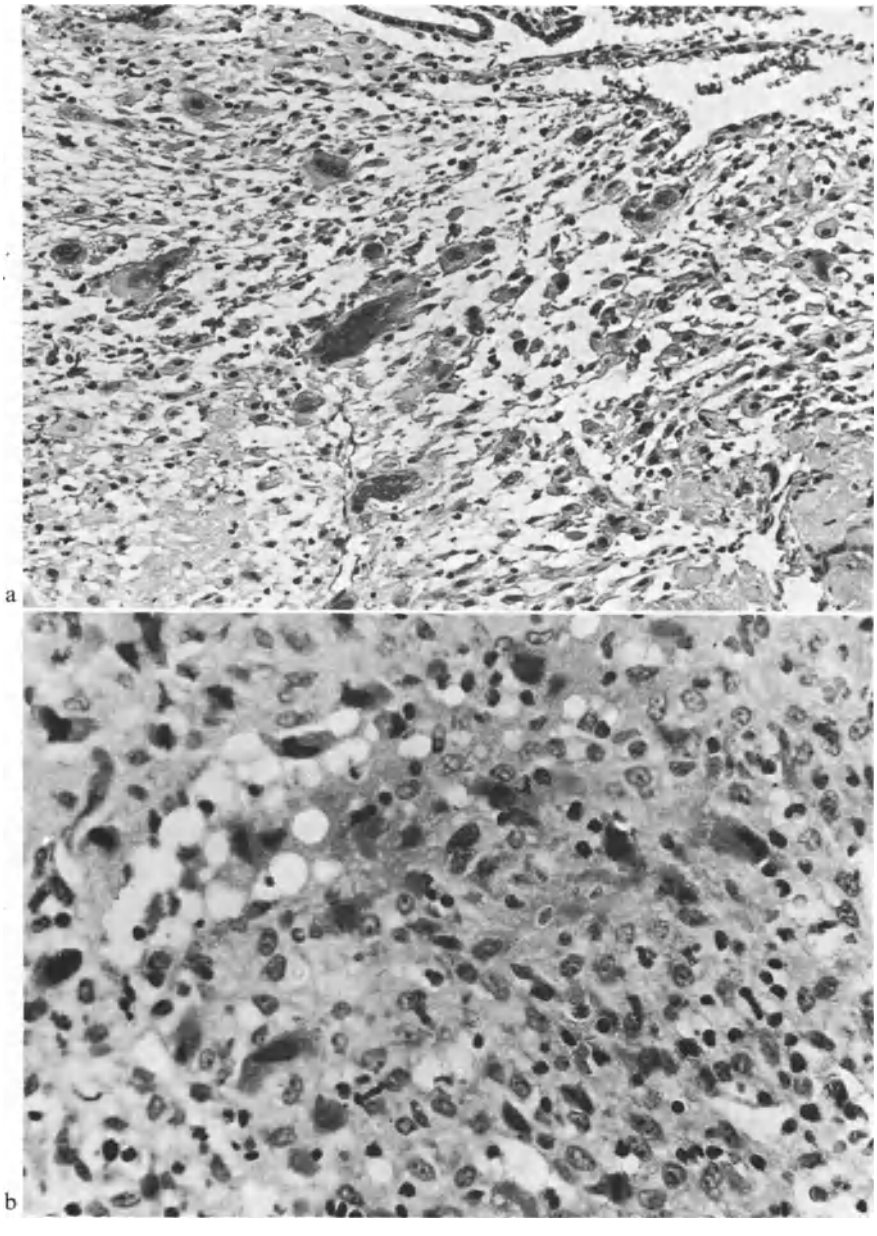


Fig. 131 a and b. Chorial invasion of the decidua. (a) Multinucleated syncytiotrophoblast, (b) cytotrophoblasts with single nuclei

those of the hydatidiform mole in two respects, which we use as diagnostic criteria. First, although the villi of a blighted ovum are swollen and their mesenchymal fibers loosely dispersed by the edema, they never contain large central cystic spaces as do the villi of hydatidiform moles (Fig. 139). Second, the trophoblasts ensheathing the villi of blighted ova are atrophic or degenerating. In contrast,

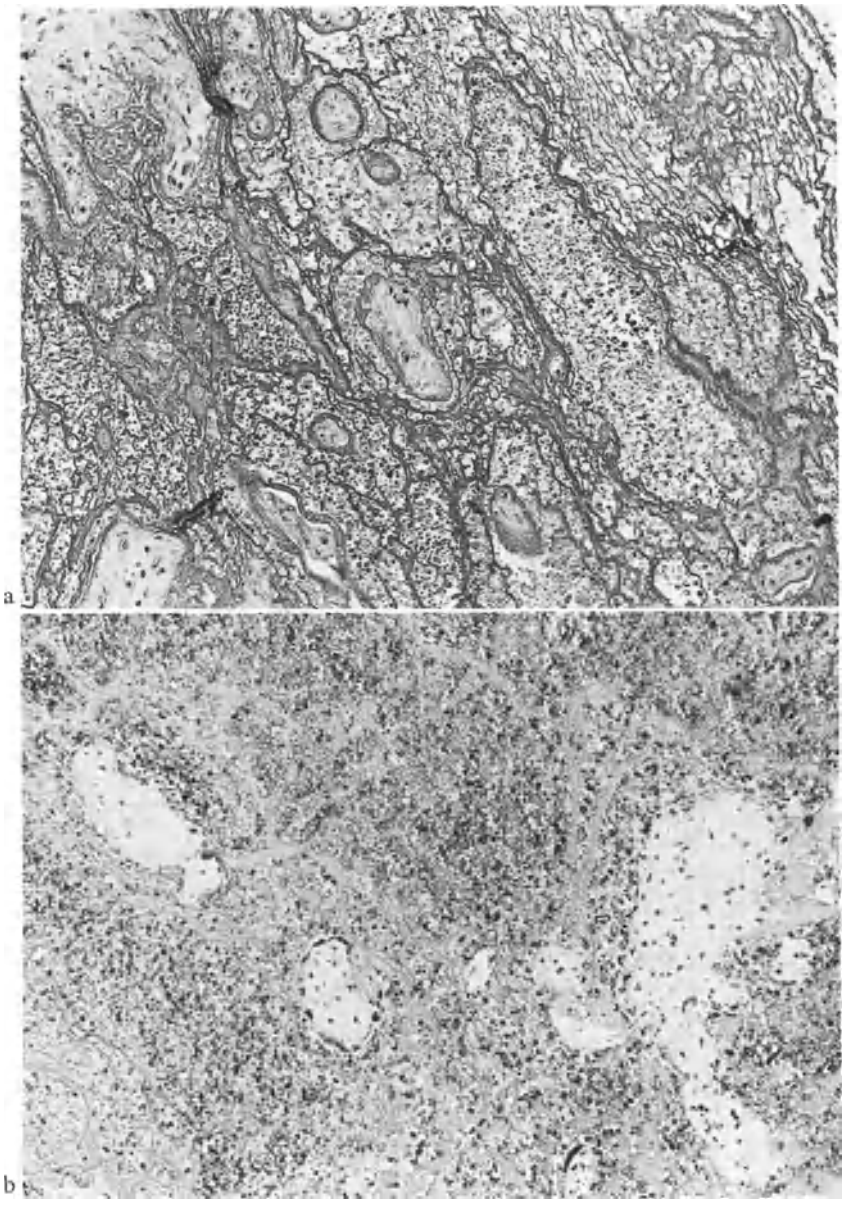


Fig. 132 a and b. Necrotic placental villi immured in fibrin (a) and blood (b)

the trophoblastic cells of molar villi are usually hyperplastic, and occasionally even anaplastic. Some authorities (HERTIG and EDMONDS, 1940; HUBER *et al.*, 1957) postulate, that when a blighted ovum fails to abort, and is retained and survives, it eventually becomes a true hydatidiform mole. Proof of that theory unfortunately is still lacking. Hydropic swelling of chorionic villi most likely is etiologically related to faulty development of the embryo. According to HÖRMANN and LEMTIS (1965), such a blighted ovum is usually aborted between

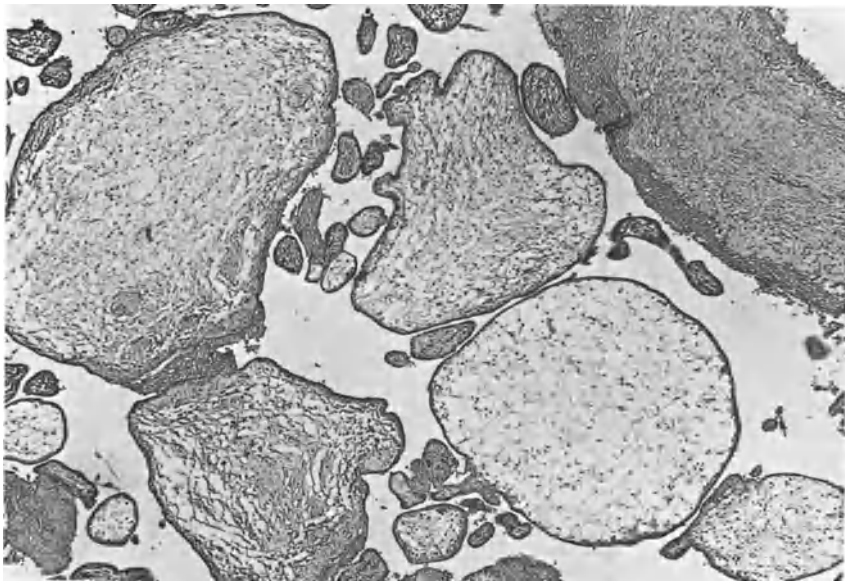


Fig. 133. Hydropic swelling of villi of a spontaneous abortion during the second month: Extremely flattened trophoblastic epithelium

the eleventh and thirteenth week; a hydatidiform mole is usually expelled after the sixteenth week.

Further structural malformations of the villi that may be recognized almost always indicate a spontaneous abortion caused by a primary defect of the embryo. Non-vascularized villi (Fig. 134) and large deposits of acid mucopolysaccharides within them (EMMERICH, 1967) point either to severe abnormality of the embryo or to its failure to develop at all. Frequently the chorionic trophoblasts are defective or even abnormally proliferated. To evaluate chromosomal anomalies, histological study of the placental villi may prove especially informative and certainly is easier to perform than the cytogenetic methods (PHILIPPE, 1973; BREUKER *et al.*, 1978). Triploidy and tetraploidy often lead to hydropic degeneration of the villi. Consequently, measurements of the DNA content of the nuclei of their stromal cells reveal equivalent polyploid sets of chromosomes. In addition, in other anomalies such as monosomy and trisomy, characteristic changes appear in the villi; for example, growths of cytotrophoblast penetrate the villous stroma and the syncytiotrophoblast becomes hypotrophic.

Other regressive changes of the villi, however, are of no help in deciding what the cause of abortion might be. For example, occasionally the collagen fibers of the villus stroma become thickened and hyalinized (Fig. 135). As these changes progress, the stromal cells and blood vessels gradually disappear. The ground substance may undergo fibrinoid or mucoid degeneration, as its metachromasia with toluidine blue or mucus stains so well demonstrates. Fibrin may also be precipitated. As GRAY (1956) suggested, the fibrinoid or hyaline degeneration of the villus stroma might be related to an incompatibility between mother

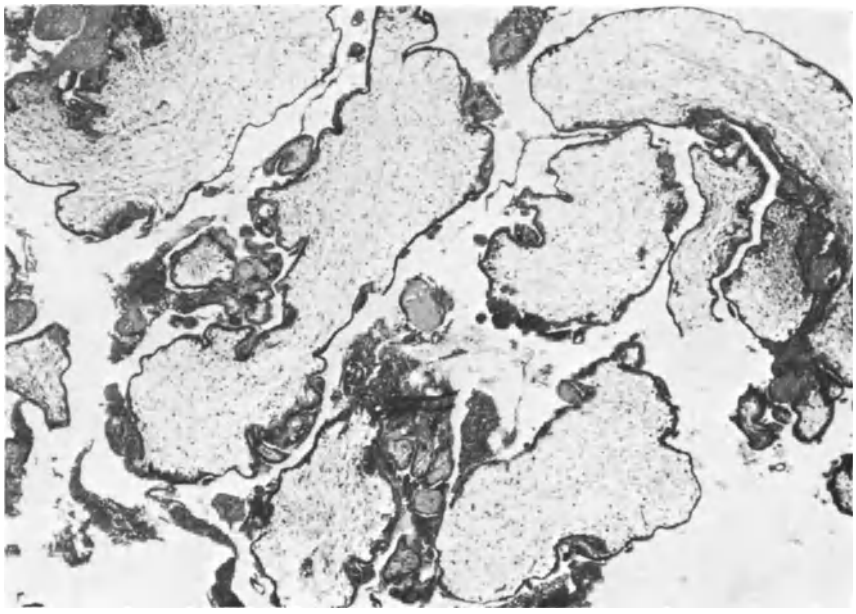


Fig. 134. Large avascular villi of spontaneous abortion during third month

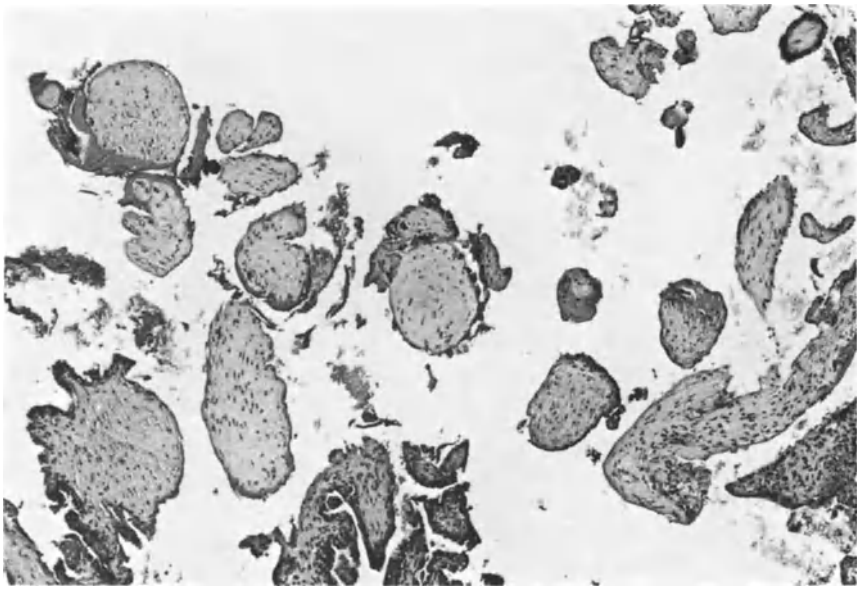


Fig. 135. Fibrosis of villi of a spontaneous abortion during the third month

and fetus. In addition, one may find nucleated erythrocytes in the capillaries of the villi later than normal (GERDES and SCHULTE, 1966). No attempts should be made to correlate the number of Hofbauer cells with a malformation since the function of these cells remains unknown. As ECKMAN and CARROW (1962)

noted, in all forms of abortion the structural changes may vary strikingly from villus to villus, the differences depending qualitatively and quantitatively on how long the products of conception are retained.

The solutions injected into the amnion **to induce abortion** (saline, rivanol, prostaglandins) cause degenerative changes in the villi and decidua, stasis of blood in the intervillous spaces, and thrombosis and hemorrhage in the decidua basalis and marginalis. After saline solutions the fetal membranes may become edematous and the subchorial tissues necrotic (HONORE, 1976; PURI *et al.*, 1976). After curetting the endometrial cavity, bleeding is better stanched than after a normal delivery, since the curette produces a profuse exudation of fibrin, which rapidly coats the wound. The spiral arteries become plugged with aggregates of platelets and fibrin. Endothelial proliferations, decidual cells and the trophoblast involute (SLUNSKY, 1976).

If the embryo were **aborted** or expelled **months before,** then a retrospective explanation of why it did so may prove impossible. Usually in such cases the placental villi cannot be demonstrated. Fragments of *decidua* may also be lacking, or if present, they appear as completely hyalinized, nodular or garland-shaped remnants about spiral arterioles that are still large and conspicuous (Fig. 136). At times in these homogeneous, pale-staining regions of stroma one may discover barely recognizable remains of single decidual cells, enough evidence, however, to point to what kind of change has taken place. Now and then trophoblastic cells may remain visible in these regions for several months. Ultimately with complete hyalinization these portions of endometrial stroma resemble a small corpus albicans of the ovary. If these decidual remnants are absent, however, then only a presumptive diagnosis can be made of suspected previous abortion. Since that diagnosis carries implications that may be of utmost importance for the patient, yet about which the pathologist may know nothing, he should exercise great prudence in making it, and if possible confer with the patient's physician.

The *endometrium* about decidual remnants almost always shows an infiltration of inflammatory cells (endometritis post abortum), and often is still undergoing irregular shedding. At a later stage a new proliferative phase may predominate. Since that proliferation may at times proceed irregularly, either because decidual remnants act as mechanical irritants or because hormonal balance fails to become reestablished, histological pictures of hyperplasia (the socalled "adaptation hyperplasia" of VELTEN*) may evolve that resemble glandular-cystic hyperplasia. Hyaline deposits may appear in the stroma of this adaptation hyperplasia just as they do in other glandular-cystic hyperplasias (see p. 107). Although their causes are entirely different, these hyaline deposits of hyperplasias may be confused with hyalinized remnants of decidua. Consequently, in certain instances it may be difficult to distinguish a beginning or modified cystic hyperplasia with prominent hyaline deposits from hyalinized decidual remnants with an associated adaptation hyperplasia. If there had been an abortion, a diligent search will reveal characteristic stigmata of the previous pregnancy: unaltered groups of hypertrophied spiral arterioles and at times single involuted glands showing persistent secretory changes. Besides the infiltrates of inflammatory cells in the

* Personal communication.

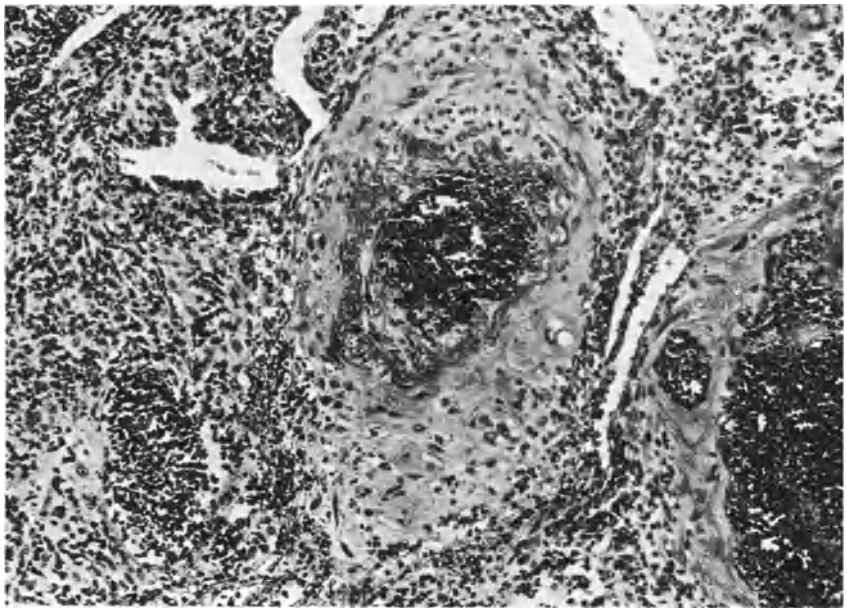


Fig. 136. Garland-like remnants of decidua near dilated stromal vessels several weeks after an intrauterine abortion. The surrounding endometrium is involuted and infiltrated with chronic inflammatory cells: endometritis post abortum

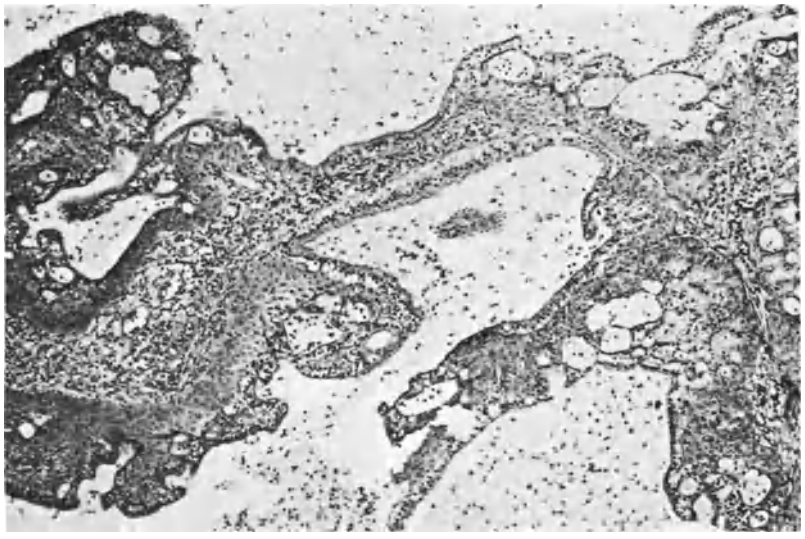


Fig. 137. Endocervicitis post abortum with extensive squamous metaplasia

endometrial stroma, groups of hemosiderin-filled macrophages may be found that otherwise are rarely seen (HINZ and SOLTH, 1959).

A curettage performed after an abortion often yields many fragments of tissue from the proliferated and papillary *endocervical mucosa*. Histologically, the

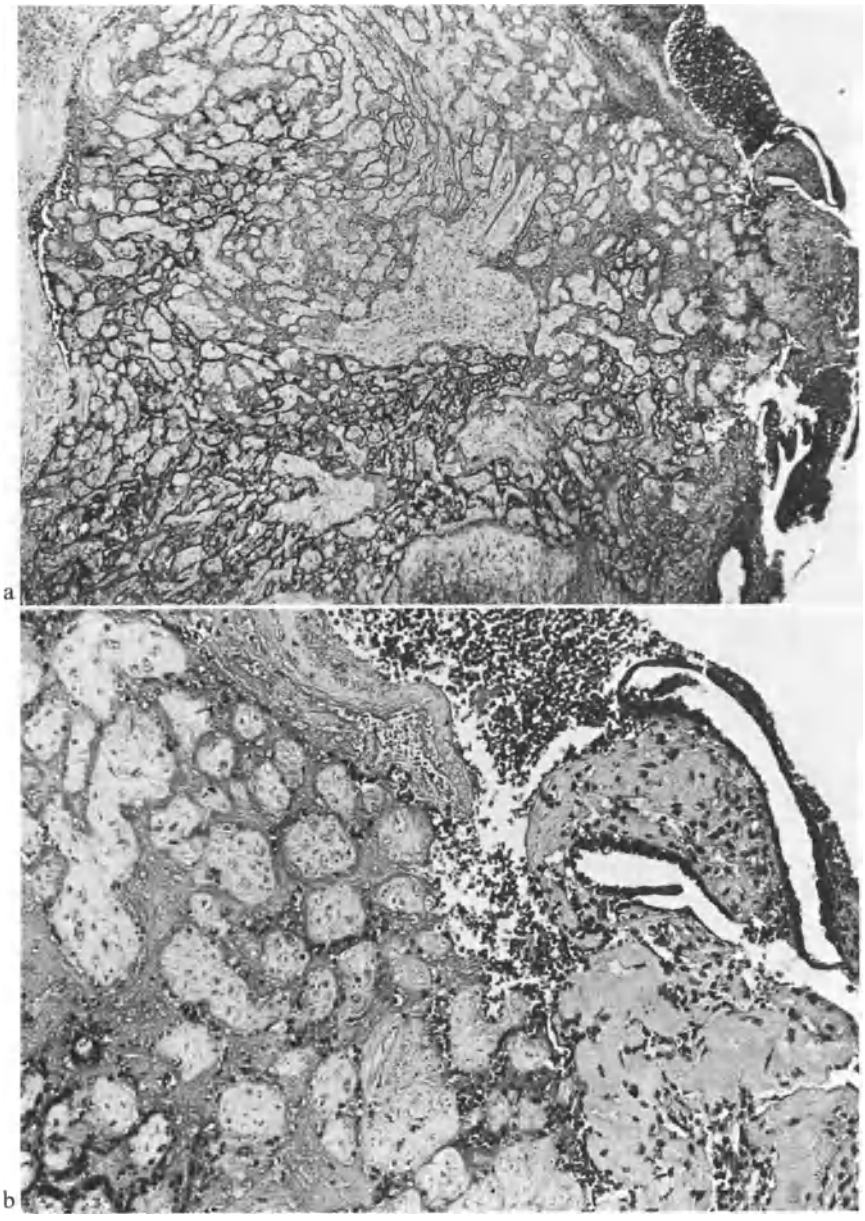


Fig. 138a and b. Placental polyp. (a) Low magnification. (b) Higher magnification

fragments show the characteristic glandular hyperplasia, squamous metaplasia and vacuolization of the epithelial cells that develop with pregnancy (MEINRENKEN, 1956; Fig. 137).

If, after abortion, portions of the placenta remain attached to the decidua or directly to the myometrium they prevent the endometrium from regenerating and usually cause protracted bleeding. The retention of placental tissue occurs oftener in women who have injured their endometrium by antifertility agents

or intrauterine devices than in women who have never used these agents (REYNIAK *et al.*, 1975). As fibrin and coagulated blood accumulate about the retained tissues, a protuberant mass gradually develops, a socalled **placental polyp**, which may occasionally reach the size of a hen's egg and become quite firm. Eventually the polyp disintegrates at its attachment and is cast off with a lochial discharge. Its center usually consists of necrotic villi but also at times of fairly well-preserved villi and trophoblastic cells (Fig. 138). From histologic studies we know such trophoblastic cells may survive for long periods. Placental polyps removed several years after the last pregnancy may still contain intact, viable-appearing trophoblasts. Villi, although hyalinized, kept their characteristic shape and structure and could be identified in a placental polyp retained for twenty-one years (SWAN and WOODRUFF, 1969).

Several authors have reported finding portions of *cartilage and bone* in surgically removed uteri, and have postulated that these foreign tissues represented dystrophically calcified remnants of fetal tissue and bone from one or more abortions months to years before (DE BRUX *et al.*, 1956; see here for earlier literature; ROBINSON, 1964; NEWTON and ABELL, 1972). Others were of the opinion the cartilage and bone represented a reaction to the chronic inflammation associated with the abortions (GANEM *et al.*, 1962; HSU, 1975). In contrast, from the study of two such cases MEYER-FÜRST (1961) thought the osseous-chondral tissues had resulted from previous hysterography. BANIECKI (1963) described plates of cartilage enclosed by normal endometrium. He regarded the cartilage as altered remnants of retained menstrual tissues, since he believed cartilaginous products of conception should be surrounded by an inflammatory reaction. Finally, ROTH and TAYLOR (1966) maintained that mature stromal cells were capable of cartilaginous metaplasia. In nine endometria containing cartilage they were able to exclude the possibility that fetal parts had been retained. They succeeded in demonstrating focal concentrations of acid mucopolysaccharides, which they interpreted as transitions in the formation of cartilage. They might have seen, however, a benign teratoma of the endometrium (see p. 161). In the differential diagnosis it is necessary to rule out a malignant mixed Müllerian tumor of the uterus that produces neoplastic bone and cartilage. — Several reports of **glial tissue** in the endometrium have stimulated various interpretations. ZETTERGREN (1956, 1973), URBANKE (1962), VANEK and LANE (1963), STOLZ *et al.* (1964), HANSKI (1971) and NIVEN and STANSFELD (1973) thought the glial tissue they found represented remnants of fetal tissue from a previous abortion, implanted in the uterus during curettage. Implanted glial tissue may remain active for a long period and may proliferate, perhaps because of its known low concentration of isoantigens. HAMPERL *et al.* (1959) agreed that fetal glial tissue lodged in the endometrium most likely is able to grow independently; they also discussed the possibility, however, of pluripotent cells arising locally to grow autonomously like tumor cells, a hypothesis with which BAZALA (1966) concurs.

c) Hydatidiform Mole and Choriocarcinoma

Even to now the question remains unanswered whether we should class the **hydatidiform mole** by virtue of its growth potentialities and its tendency to be

a precursor of choriocarcinoma, with true neoplasms, or whether, as HERTIG and EDMONDS (1940) have done, we should regard it as a temporarily retained blighted pregnancy with advanced hydropic swelling of the chorionic villi and variably proliferated trophoblastic cells. According to CARR (1969), hydropic change, hydatidiform degeneration of villi, and a typical mole have common cytogenetic and pathologic characteristics which overlap. All these conditions commonly reveal chromosomal anomalies, generally triploidy, which seems typical of the hydatidiform mole. The degree of hydatidiform change depends on the maturity of the placenta; that is, as the pregnancy advances the villi enlarge. It is now usual to distinguish two forms: in the *partial hydatidiform mole* the hydropic swelling evolves in only one part of the placenta; bordering the swollen beadlike villi are normal villi. The trophoblast is only slightly proliferated. The embryo is generally present and triploidy is usually found. In contrast, in the *complete hydatidiform mole* the vesicular swelling and villous degeneration develop diffusely and rapidly. The trophoblast proliferates excessively. The embryo is absent, and the chromosome sets are diploid (VASSILAKOS *et al.*, 1977; SZULMAN and SURTI, 1978). When the fetus of a blighted ovum dies early or fails to develop, the blood vessels of the chorionic villi degenerate, leaving the villi with no means by which they can rid themselves of the abundant fluid passed into them by the trophoblasts. As fluid accumulates, the villi swell, ultimately ballooning-up to grape-like vesicles. The concomitant proliferation of the trophoblasts may be attributed to a stimulating effect of maternal blood on these cells. They resemble the immature trophoblasts that invade to form the solid anlage of the primordial chorionic villi.

As early as 1895 MARCHAND, [and soon thereafter LANGHANS (1901)], thoroughly described these histological changes in the hydatidiform mole. Initially the ground substance of the villi becomes water-logged and homogeneous. The mesenchymal connective tissues gradually disappear and the blood vessels fail to develop. With time the villi swell to enormous sizes. Through coalescence of small vacuoles of edema fluid large cystic spaces form, expanding to compress the surrounding mesenchymal cells so flat these seem to line the cysts like endothelial cells (Fig. 139). Both layers of the trophoblastic cells covering the villi, but especially the syncytiotrophoblasts, possess enlarged pleomorphic nuclei and proliferate intensely, usually as irregular nodules or as club-shaped masses (Fig. 140). Accordingly, the titer of gonadotropin is elevated (as compared with other moles or malformations, KAESER, 1949), and an Arias-Stella phenomenon may be demonstrated (see ROACH *et al.*, 1960; WYNN and HARRIS, 1967). Vacuoles, varying from small to large and clustered together, often appear in the syncytiotrophoblasts. Their vacuolated state resembles the formation of lacunae during early chorial invasion when the primordial villi develop. The trophoblastic cells proliferate most at the placental site of attachment. The surrounding decidua often reveals an invasion by chorionic elements that may extend down to the myometrium, a condition once referred to as syncytial endometritis. This invasion, however, does not differ from that occurring during normal placentation.

It may be quite difficult to *predict from histological sections* how a hydatidiform mole will behave biologically or what its *prognosis* will be. It is advisable to take samples of tissue from different regions, particularly where portions of

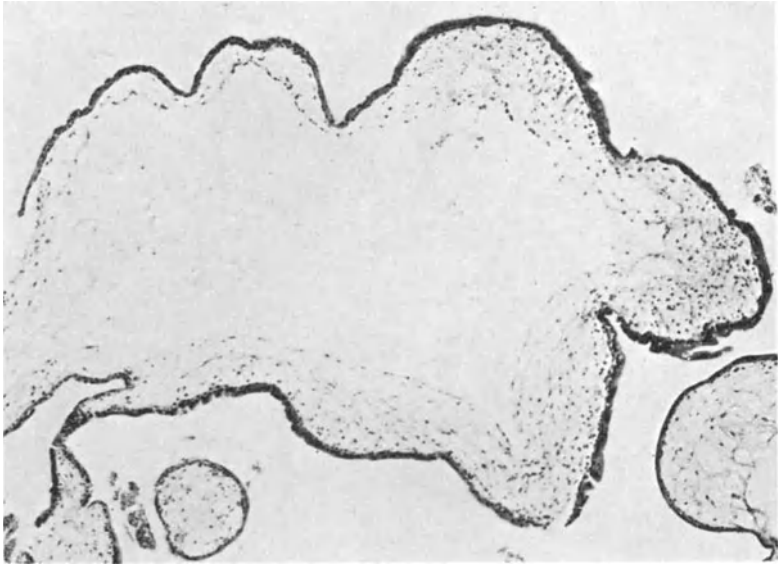


Fig. 139. Hydatidiform mole. Hydropic swelling of villi with central, cystic spaces lined by endothelial-like cells

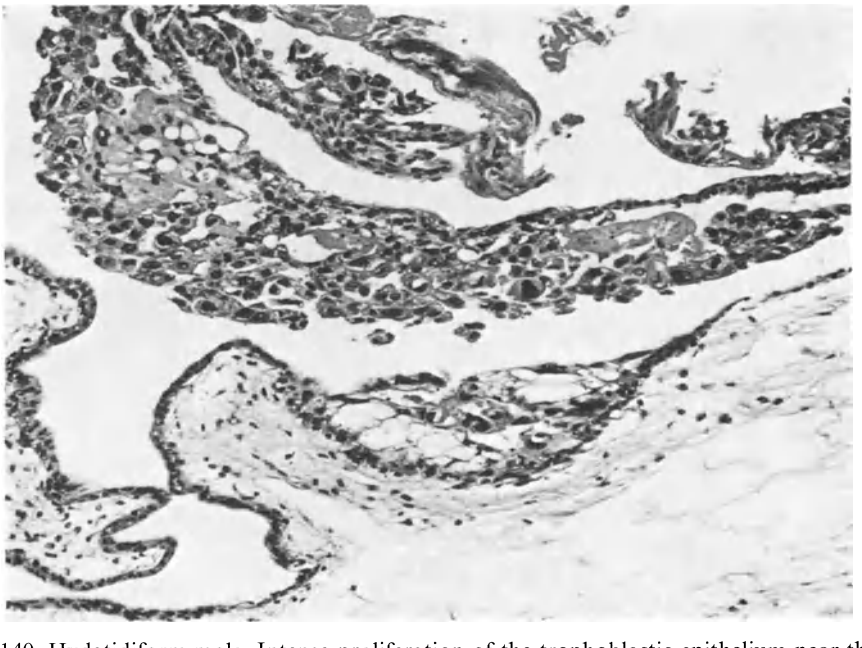


Fig. 140. Hydatidiform mole. Intense proliferation of the trophoblastic epithelium near the cystic villi

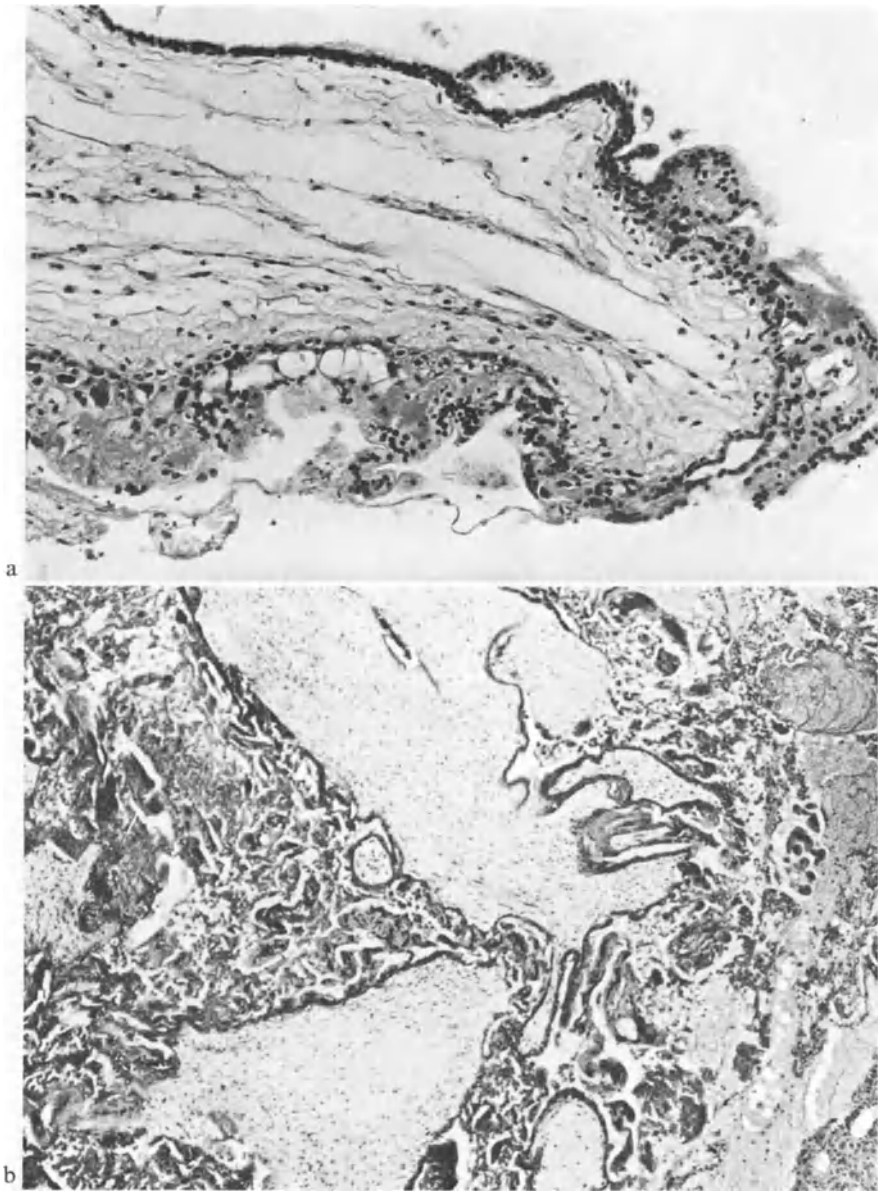


Fig. 141a and b. Invasive hydatidiform mole, with pronounced proliferation of the trophoblastic epithelium. (a) High magnification. (b) Survey view

decidua or blood clot are found (HERTIG and MANSELL, 1956). The potentially malignant quality of the trophoblastic cells is especially difficult to judge, since these cells normally are invasive. Contrary to the opinion of some authors (VASSILAKOS *et al.*, 1977), malignant transformation can occur not only in complete hydatidiform moles but also in placentas with partial moles (SZULMAN

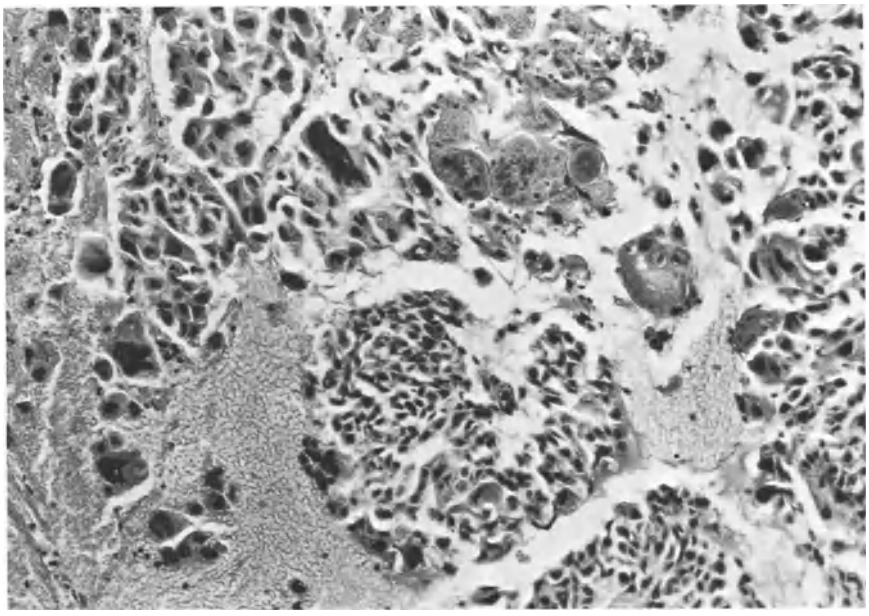


Fig. 142. This chorionepithelioma appeared twelve weeks after an invasive hydatidiform mole

and SURTI, 1978). The degree of trophoblastic proliferation, a criterion often used for the histologic grading of hydatidiform moles, is of little value in evaluating prognosis. Statistics indicate that more patients with a grade I mole (with little to no hyperplasia of the trophoblast) later develop a choriocarcinoma than do patients with a grade II (moderate hyperplasia) or grade III (intense hyperplasia with anaplasia) mole (ELSTON and BAGSHAWE, 1972). Consequently, in the clinical follow-up of patients who had a hydatidiform mole it is important that their gonadotropin levels be determined. Electron-microscopically some moles resemble choriocarcinomas, e.g., the cells of the trophoblast are poorly differentiated. When these changes progress, they may herald the development of a choriocarcinoma. About 50 per cent of all choriocarcinomas arise from hydatidiform moles. On the other hand, in European populations, only about two per cent of hydatidiform moles are followed by choriocarcinoma (RINGERTZ, 1970).

If such sheets or clumps of cells invade the myometrium, or villi and free trophoblastic cells are found growing within a myometrial blood vessel, then it seems justifiable to diagnose an *invasive mole* (chorioadenoma destruens). The main difference is in the quantity of proliferation; the trophoblastic cells still resemble those of a benign hydatidiform mole (Fig. 141). Although the entire myometrium may be invaded, the prognosis nevertheless is usually good. The diagnosis, however, can rarely be made from curettings; one usually needs the resected uterus to determine the extent of growth.

Choriocarcinoma in curettings generally consists of solid or plexiform cords or clumps of poorly differentiated trophoblast cells with hypertrophied irregular

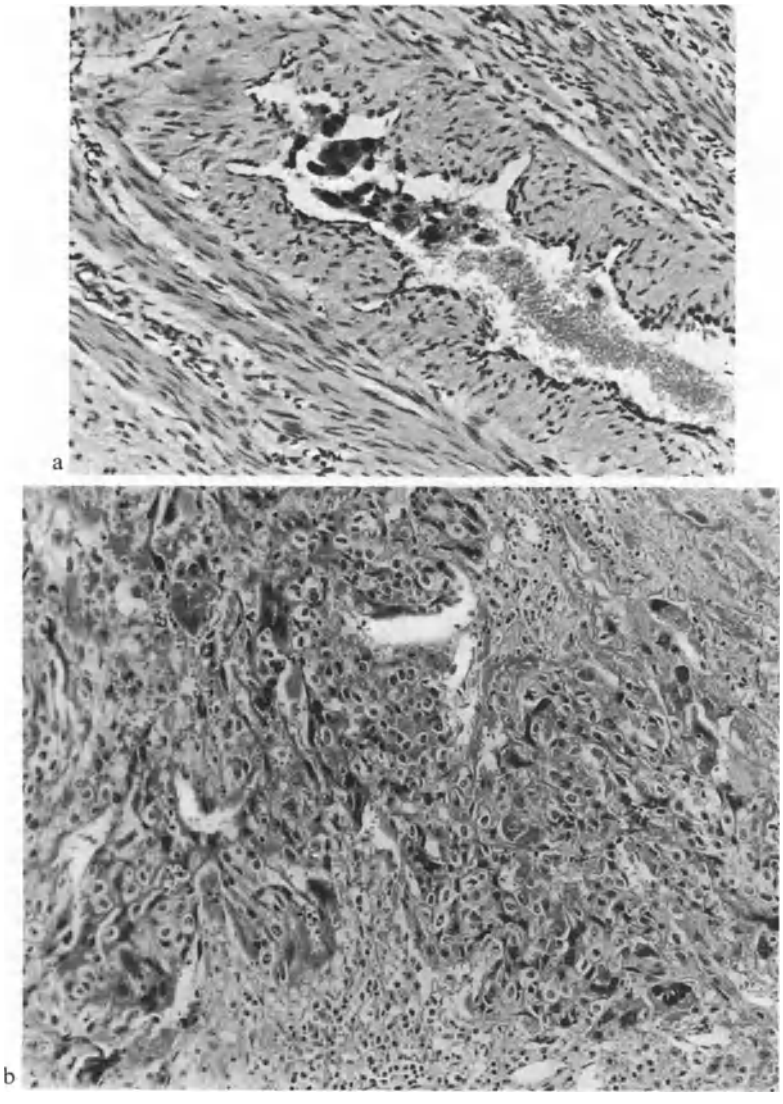


Fig. 143 a and b. Same case as in Fig. 137. Invasive growth with penetration: (a) of a vessel and (b) of the myometrium

nuclei and with high growth potentialities, as suggested by their restless, disorderly appearance. Placental villi are usually absent. The cords of tumor, admixed with necrotic decidua and clotted blood, may be composed of only cytotrophoblasts or syncytiotrophoblasts. Occasionally the two intermingle with one another. The atypical cells that are always present are easier to detect among the cytotrophoblasts than among the syncytiotrophoblasts, which even normally exhibit great variation in size of cell or nucleus (Fig. 142). Cells of choriocarcinomas electron-microscopically differ from the normal trophoblast only by their deeply

indented nuclear membrane, their large nuclear pores, their irregularly shaped mitochondria, their scanty endoplasmic reticulum, and their RNA granules lying free throughout the cytoplasm (LARSEN, 1973; previous literature see there). The choriocarcinoma usually develops weeks after abortion at the site of placental attachment. From there it invades the myometrium and its vascular channels (Fig. 143). Consequently, the curettings frequently contain fragments of myometrium, which in contrast to those of benign chorial invasion, are penetrated and compressed by hyperplastic rows of atypical, anaplastic trophoblasts, causing necrosis and hemorrhage. The maternal tissues appear to be unable to mobilize any defense mechanisms (for example, immune cell response). Diagnosis of a frank choriocarcinoma seldom constitutes a problem. At times, however, the malignant chorial invasion may be exceedingly difficult to distinguish from a benign invasion (for example, that of the invasive hydatidiform mole). An important criterion of benign invasion is the advance of individual cells along preformed clefts in the tissue without encroaching upon or injuring adjacent muscle cells. A common mistake is to over-evaluate a benign hydatidiform mole and diagnose it as a choriocarcinoma (NOVAK, 1953; HERTIG, 1968; BAGSHAWE, 1969). Such a diagnosis is justified only when the histological sections reveal extensive necrosis of tissue in the absence of chorionic villi and when the biological behavior of the tumor suggests it is malignant (e.g., high levels of gonadotropins, clinical history of persistent bleeding, subinvolution of the uterus). SCHOPPER and PLIESS (1949) drew attention to these differences and accordingly proposed that the clinically benign chorial invasion of the myometrium be called a "chorionepitheliosis" to clearly separate it from the choriocarcinoma. During delivery, groups of trophoblastic cells may lodge in the cervix or vagina and grow to produce nodules which give the false impression of a metastatic choriocarcinoma. These nodules of displaced trophoblast are referred to as benign chorionepitheliosis externa. On the other hand, a choriocarcinoma may be so poorly differentiated that it does not produce gonadotropin; consequently, gonadotropin levels remain low and are of little diagnostic value in these tumors.

The prognosis of a true choriocarcinoma is usually very poor. The five year survival rate in RINGERTZ's series was 50 per cent, but for those without preceding mole only 14 per cent. Newer chemotherapeutic regimes, especially those employing amethopterin (Methotrexate), have proved highly effective in curing patients of the disease.

2. The Endometrium Associated with Extrauterine Pregnancy

The decidua developing during an extrauterine pregnancy *with viable fetus* differs from that formed during a normal uterine pregnancy only by the absence of trophoblasts, chorionic villi and associated reactions in the adjacent stroma (formation of a hyaline-fibrinoid boundary) and blood vessels (dilatation prior to formation of intervillous spaces). Enlargement of the decidual blood vessels associated with an extrauterine pregnancy develops only at the onset and is never pronounced (SPEERT, 1958).

After death of the fetus of an extrauterine pregnancy the decidua regresses. The regression however proceeds gradually, because the hormone-secreting chorionic villi in the wall of the fallopian tube insure that the corpus luteum involutes only very slowly. In addition, because the endometrial cavity contains no dead fetus, it remains free of any significant inflammation. Consequently, the decidua rarely is spontaneously expelled; instead it regresses and because the next ovulation may be greatly delayed (OVERBECK, 1953), the endometrium may actually atrophy. With gradual and ultimate, severe shrinkage of the stroma, the *glands* collapse. These often exhibit the Arias-Stella phenomenon, their lining cells possessing swollen, clear cytoplasm and large, grotesque nuclei. Since the phenomenon generally develops focally, its incidence as reported by different authors varies, depending upon the precision and care exercised in examining the endometrial curettings. The *decidual cells* also shrink, eventually being no larger than the endometrial granulocytes, which seem to increase in number because the decidual cells become smaller. The granules of the endometrial granulocytes, however, do increase in size and number. An extremely dense network of reticulum fibers forms around the decidual cells. To demonstrate that network methods of silver impregnation are ideal. As the ground substance loses acid mucopolysaccharides, it becomes distinctly fibrous (OVERBECK, 1962). Consequently, the groups of spiral arterioles that had failed to involute become more prominent than ever. While these changes progress, a few regions of the decidua begin to disintegrate and become necrotic. In contrast, other regions will have lost their decidual character because of severe shrinkage. The picture histologically as well as hormonally represents that of irregular shedding. If the decidual cells complete their retrogressive changes, becoming once again small and spindly, then the glands lined by large clear epithelial cells (Arias-Stella phenomenon) may be the only evidence of the foregoing pregnancy (FREDERIKSEN, 1958). In other words, the regression of the stroma regularly precedes that of the glands.

Such changes may still be evident many weeks after the abortion. As a new follicle proceeds to maturity (about one month after onset of bleeding; according to BANIECKI, 1953, no earlier than 6–7 weeks after death of the fetus) the endometrium begins to proliferate anew. During that process of regeneration the old portions of mucosa gradually become incorporated or replaced by the new tissues; the exact mechanisms involved in the replacement, however, escape detailed histological analysis. As the Arias-Stella phenomenon slowly abates, the epithelial cells of the glands flatten out; their cytoplasm becomes vacuolized and their polymorphic nuclei shrink. Although involution may be extreme, some glands continue to retain abnormal amounts of glycogen (CRAMER, 1957). When these terminal changes of the glands finally disappear and the new proliferation dominates the picture, it becomes impossible to even suspect that there had been a preceding pregnancy. The endometrium then may resemble that of an anovulatory cycle, although there still may be clinical signs of a previous extrauterine pregnancy.

The clinically important and therefore much-discussed question of whether it is possible from curettings *to differentiate between an extrauterine pregnancy and an intrauterine* cannot always be answered decisively, even when all available special histological methods are employed. A clear-cut decision is feasible only when one finds fetal tissues (chorionic villi or trophoblasts). If these are not

found, even though new step-sections of the tissue have been examined, then the best one can do is make a diagnosis of probable extrauterine pregnancy, basing that decision on the fact that the decidua of an extrauterine pregnancy involutes very slowly and rarely reveals inflammatory changes. Occasionally, however, a severe endometritis may accompany an acute salpingitis, which is the cause of the extrauterine pregnancy. That its involution is greatly retarded is indicated, first, by the increased numbers of "collagen inclusions" in the decidual cells. Another indication is the failure of the decidua to shed, thus allowing the decidual cells to shrink severely; and third, the greatly delayed regeneration by the endometrium. In addition, the Arias-Stella phenomenon serves as evidence that the embryo has died and gonadotropin is still being produced by placental tissues, which may remain viable for a long time. These placental tissues more commonly belong to an extrauterine pregnancy than to an intrauterine (67 per cent against 43.6 per cent, according to OVERBECK, 1962; see also BEATO *et al.*, 1968). The differences here between the two types of pregnancy are quantitative, not qualitative. According to MEINRENKEN (1952) and HOMMA (1958) hyaline rings more often develop around the capillaries of the involuting compacta of intrauterine pregnancies than of extrauterine. They do develop however in the extrauterine pregnancies. On the other hand, the extrauterine implantations often lack the hemosiderin deposits and fibrinoid exudates found in the stroma of intrauterine pregnancies (HINZ and TERBRÜGGEN, 1952). No histochemical reaction exists that accurately distinguishes between the endometria of intrauterine or extrauterine pregnancies (LEWIN, 1960). Attempts to differentiate the two seem all the more futile when one considers that the changes occurring in the endometrium may vary greatly, depending upon the type, extent and time of disturbance befalling the extrauterine or intrauterine pregnancy (see ARRONET and STOLL, 1950). For example, sudden rupture of the tube may cause the decidua to rapidly degenerate, or intrauterine abortion may be unusually prolonged. A review of 1,000 tubal pregnancies from the literature (OVERBECK, 1962) disclosed that curettage yielded decidua in only 43 per cent (according to ROMNEY *et al.*, 1950, in only 19 per cent). Since almost any endometrial change may develop with an extrauterine pregnancy, even a glandular-cystic hyperplasia (KIEF and MUTH, 1951) or socalled "adaptation hyperplasia" (VELTEN) or even an endometrial atrophy remaining refractory after therapy with antifertility agents, then one is not justified in reporting from the curettings alone that no extrauterine pregnancy exists merely because one finds no fetal tissues (see BRUNTSCH, 1954). In problem-cases the detection of fetal tissues may be of decisive importance (HOFMANN and LEGERLOTZ, 1968). We help the attending gynecologist considerably in doubtful cases even when we report no more than "suspicion of intrauterine pregnancy" or "extrauterine pregnancy unlikely". He will be able to modify his care of the patient accordingly. After curettage, persistent bleeding indicates that an extrauterine pregnancy undoubtedly exists, the blood emanating from the site of placental implantation in the wall of the fallopian tube (BRUNTSCH, 1954). In such instances the clinician is responsible for the final diagnosis, not the pathologist.

Decidua without pregnancy. If one detects decidua in curettings but finds no fetal tissues, then the diagnosis of possible intrauterine or extrauterine preg-

Table 20. Source of Decidua

	Intrauterine Pregnancy	Ectopic Pregnancy	Arrested Secretion (hormonally induced)	IUCD (mechanically induced)
Last menstrual period	more than 4 weeks ago	more than 4 weeks ago	more than 4 weeks ago	*less than* 4 weeks ago
Glands	high secretion, occ. Arias-Stella	high secretion, occ. Arias-Stella	*atrophic*	high secretion, occ. Arias-Stella
Extent of decidualization	complete	complete	complete	*focal*
Inflammatory infiltration	present	*none*	none	present
Fetal elements	*often present*	none	none	none

nancy may be made, but only with reservations. In BOBEK's series of patients (1957) the suspicion of extrauterine pregnancy based on the presence of decidua alone proved correct in only 20 per cent. Just as the lack of decidua is poor evidence for proving the absence of an extrauterine pregnancy, so is the presence of decidua little proof that a pregnancy does exist. A large cyst of a corpus luteum or a persistent corpus luteum may induce a decidual change in the endometrium that is histologically identical with the decidua of a young intrauterine or extrauterine pregnancy (TE LINDE and HENDRIKSEN, 1940; ISRAEL, 1942; SPECHTER, 1953). It may be that in such cases an overproduction of gonadotropin induces not only the cyst of the corpus luteum but also the decidual change of the endometrium. Other causes of decidual change in the absence of pregnancy are granulosa-cell tumors and certain hormone-secreting carcinomas of the ovary (SPECHTER, 1953). Therapy with gestagens (for example, for endometriosis) may also lead to the development of decidua, which however differs from that of pregnancy since it lacks secreting glands. If glands are present in these decidua, they are atrophic ("starre Sekretion" = "arrested secretion"). All these causes explain why from time to time we may observe an intrauterine decidua in old women (see p. 198, p. 222, and Fig. 109). Decidual change may also be provoked by mechanical stimulation and closely resemble the deciduomas of rats and mice that are readily induced by trauma. Characteristic of the mechanically produced decidual change is its localized development; for example, its adjacency to a non-medicated intrauterine device (see p. 250). It is very important for the clinician to know what type of decidua is present and how it was induced. The differential diagnosis therefore should be given careful thought. Characteristics that may help in reaching a definitive diagnosis are listed in Table 20.

3. The Postpartum Endometrium

Within ten days after delivery, the inner surface of the uterus is covered again by an unbroken layer of epithelial cells that grow out from the stumps of glands

in the basalis. Within three to five weeks post partum the regeneration is completed. The blood vessels at the site of placental attachment become occluded by constricting, and by endothelial proliferation, thrombosis, and hyaline degeneration. As the underlying endometrium proliferates, these vessels and the surrounding remnants of decidua become sequestered from the uterine wall (Fig. 144). After six weeks only deposits of hemosiderin are evident. After three months the site of placental attachment usually cannot be recognized; not even scar-tissue

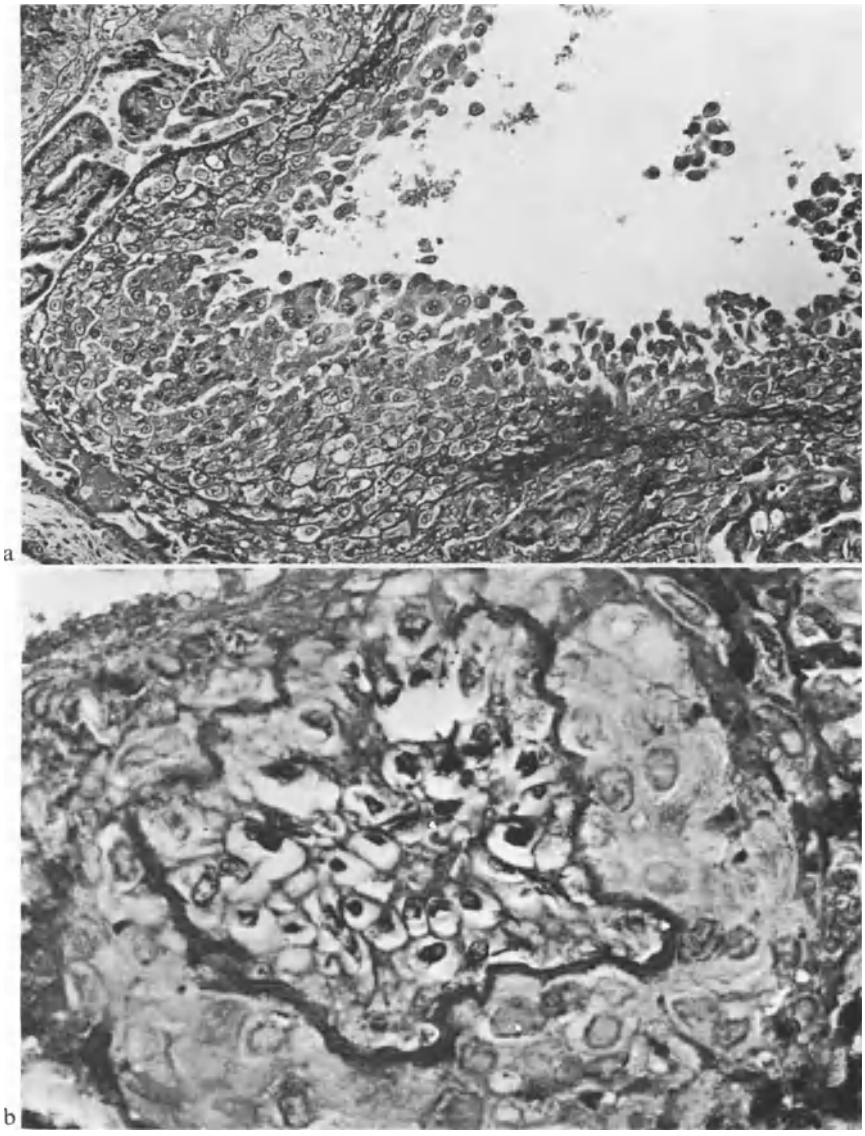


Fig. 144 a and b. Endothelial proliferation within a thin-walled vessel at the site of separation of the placenta (a), and in the placental bed post partum (b)

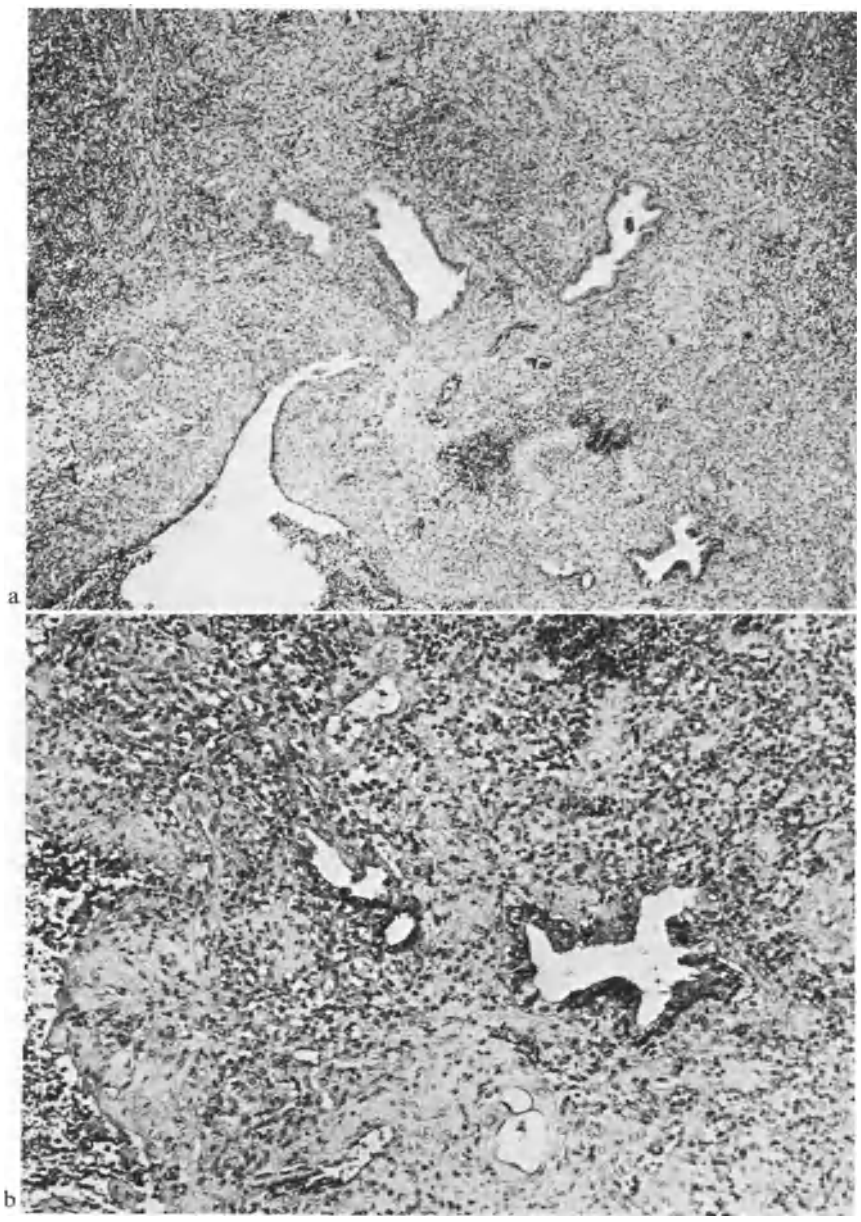


Fig. 145a and b. Endometritis post partum. Focal infiltrates of polymorphonuclear leukocytes, lymphocytes, and plasma cells with destruction of glands. The glands are still involuting and star-shaped. (a) Survey view. (b) Higher magnification

remains. BÜTTNER (1911) reported, however, he was able to detect hyaline changes in the placental bed up to one year after delivery. If mothers do not breast-feed, the endometrium reaches an advanced proliferative phase by the third post partum week (VOKAER, 1956). Breast-feeding, on the other hand, greatly retards the

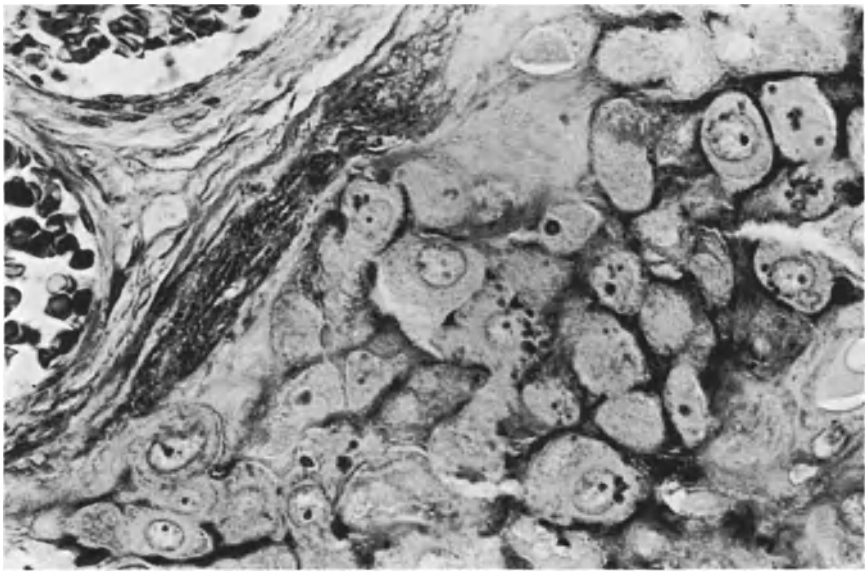


Fig. 146. Relaxin-containing cells of the basal plate of a mature placenta. The granules correspond to the paranuclear granules of the endometrial granulocytes. Phloxine-tartrazine stain

proliferation; the glandular epithelium becomes only moderately high (GROSS *et al.*, 1957). Generally, women who are not breast-feeding first ovulate the seventh post partum week. Women who breast-feed usually do not ovulate before the thirteenth week (SHARMAN, 1967).

Uterine hemorrhage during the post partum period means that the endometrium is not involuting and regenerating as it should. Curettage often becomes necessary. In two-thirds of such cases the histological studies disclose that retained portions of placenta, decidua or fetal membranes are responsible for the defective involution (BACHMEYER and STOLL, 1960). The condition is referred to as "*endometritis post partum*". The remnants of retained tissue are almost always necrotic, the shape of a placental polyp, and encased in coagulated blood and fibrin, or surrounded by proliferating endometrium. The glands of the endometrium are irregularly dilated, lined by cells of variable height possessing elongated nuclei. The stroma is composed of small or spindle-shaped cells and focally infiltrated with inflammatory cells. These infiltrates migrate into and destroy the glandular epithelium and are particularly heavy around the focal necroses (Fig. 145). Frequently the curettings contain fragments of the superficial myometrium, which have become edematous and soft because of the neighboring inflamed endometrium. At times the myometrial fragments may also reveal inflammatory infiltrates or even well-preserved trophoblastic cells as remnants of the chorial invasion. The post partum retention of placental or decidual tissue regularly leads to endometritis, which resolves to heal eventually only after the retained tissues are surgically removed. In contrast, the focal infiltration of leukocytes seen in remnants of placenta or decidua expelled from the uterus shortly after

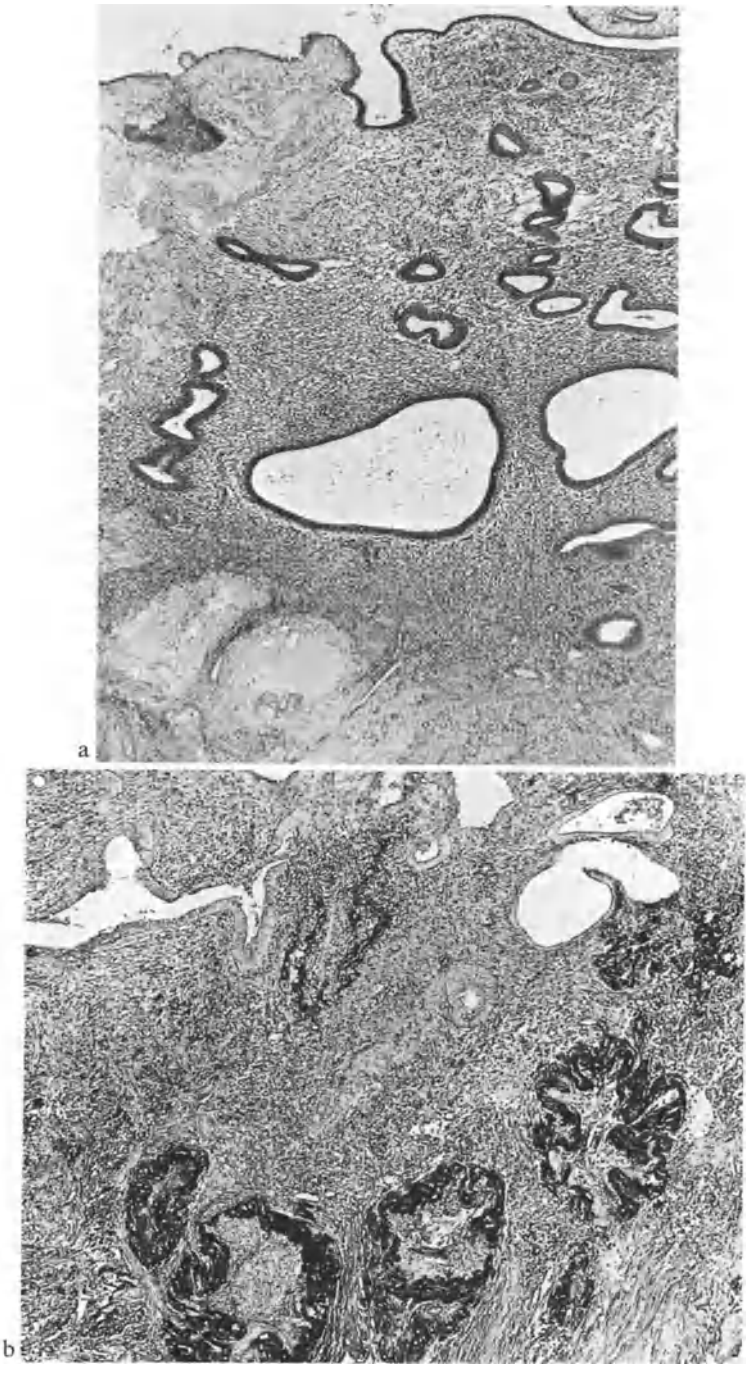


Fig. 147a and b. Post partum "adaptation hyperplasia". (a) Hematoxylin-eosin stain. (b) PAS-stain. The PAS stain reveals a garland-like ring of decidual remnants about blood vessels

delivery does not mean endometritis. Rather it represents a physiological reaction to the processes involved in detachment of the placenta at the basal plate.

The curettings of about one-third of the patients experiencing post partum bleeding (according to LESTER *et al.*, 1956, as many as two-thirds) reveal no fragments of placental or decidual tissue, or inflammatory changes that might explain the bleeding. These endometria often do disclose, however, *pathologic changes in the walls of blood vessels,* which usually are greatly dilated and congested with blood. Their walls, like many of the neighboring myometrial fibers, show hyaline degeneration; thus they are unable to contract. Their elastic fibers are destroyed. BACHMEYER and STOLL (1960) have suggested that proteolytic enzymes from the trophoblasts may initiate the hyalinization. Usually these enzymes cease to be active when NITBUCH'S stria becomes established at the basal plate. If, however, trophoblasts invade the myometrium, then because of their affinity for maternal vessels they could cause the vessel wall to hyalinize prematurely, making it impossible for the vessel later to contract effectively. In addition, the normal, relaxin-induced endothelial proliferation, which usually progresses to occlude the lumen, may fail to develop. Apparently the basal trophoblastic cells (Fig. 146), which normally can function like endometrial granulocytes, fail to release their relaxin. That failure indicates the hormonal control of placental detachment is disturbed. Such dysfunction may also be a factor in causing post partum bleeding. With the same mechanism we can explain partial uterine involution at the placental bed (BACHMEYER and STOLL, 1960; OBER and GRADY, 1961). Multipara apparently experience partial involution most often; the condition becomes more common as the number of births increases (RUTHERFORD and HERTIG, 1945), since the ability of the uterus to involute diminishes after each pregnancy.

Occasionally the first post partum proliferation develops irregularly, its glands undergoing cystic dilatation. Such changes usually ensue when an estrogen stimulus persists, as with post partum anovulatory cycles (DUBRAUSZKY, 1950). This socalled *"adaptation hyperplasia"* (VELTEN) may also cause bleeding in the post partum period (Fig. 147a). At times it may reach the severity of a glandular-cystic hyperplasia. If the patient's clinical history is not known but she is fairly young, then groups of prominent or involuting arterioles, enveloped occasionally by hyalinized remnants of decidua and found in a glandular-cystic hyperplasia (Fig. 147b), may provide an important clue to the right diagnosis. MEISSNER and SOMMERS (1950) described the changes of "adaptation hyperplasia" in diabetic women who had received estrogen and progesterone during their pregnancies.

In rare instances an irregular shedding due to a protracted fall in progesterone may result in a post partum bleeding. An insufficient or persistent corpus luteum then is more likely the cause for the slow fall in progesterone than a newly fertilized ovum.

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Subject Index

Abortion, Arias-Stella phenomenon 136, 263
—, chromosome abnormalities in 260, 270
—, criminal 259
—, decidual changes in 261
—, diagnosis of 259, 261
—, due to delayed ovulation 260
—, due to endometrial abnormalities 261
—, due to oral contraceptives 260
—, due to trophoblast abnormalities 260, 261
—, retained remnants of 272, 274, 287
—, fetal structures, diagnosis of from curettings 17, 275
—, habitual 260
—, induced 272
—, infectious causes of 261, 264
—, maternal factors 260
—, spontaneous 259, 260
—, therapeutic 257
Abortive secretion 227
Acid mucopolysaccharides, fibrinolytic inhibitors 40
— in adenocarcinoma 174
— in glandular epithelium 14, 24, 62, 131
— in glandular lumen 64
— in ground substance 35, 40
— phosphatase 27, 39, 52, 106, 131, 175, 239
Acridine orange, fluorochromation with 14, 75, 82
Actinomycosis 156
Adaptation hyperplasia 272, 283, 288, 289
Adenoacanthoma 164, 167, 168
—, development of 110, 187
—, prognosis of 178
Adenocarcinoma, cervical 164, 214
—, endometrial (see also carcinoma) 161
Adenocarcinoma arising from adenomatous hyperplasia 117, 118, 179, 193
— — —, characteristics of 118, 119
— — —, decrease in ribonucleic acid 194
— — —, histochemical studies 120, 175
— — —, irreversible change 181, 193
Adenocarcinoma in situ 181, 184
Adenoma 160
Adenomatous hyperplasia 86, 112, 114
— —, atypical glands and cells of 174
— —, change to carcinoma 117
— —, DNA of 119
— — of endocervical mucosa 244, 245
— —, evaluating prognosis of 115, 180
— —, foam cells of 114, 117
— —, misdiagnosed as cancer 172
— —, oral contraceptives and 235, 238
— —, persistent anovulation with 115
— —, precursor of carcinoma 181, 182, 193
— — due to exogenous estrogen 188, 218
— — due to unopposed estrogen 179, 193
Adenosarcoma 210
Adhesions, endometrial 256
Agonist 42
Alcian blue stain for acid mucopolysaccharides 14, 35
Aldehyde-fuchsin reaction for polysaccharides 13
Alkaline phosphatase 24, 38, 46, 47, 52, 175
—, in anovulatory cycle 99
—, in carcinoma 175
—, in deficient secretory phase 131
— in endometrial carcinoma 175
— after hormones 239
— in hyperplasia 106, 175
— phosphatases of epithelial cells 24 (see under types)
Amenorrhea, from adhesions 256
—, causes for 144, 232
—, endometrial changes associated with 97, 144
— after oral contraceptives 232, 240
—, ovarian tumours 146
—, tests in 222
—, types of 97
Aminopeptidase 40
Androstendione 192
Angiomyoma 160
Angiosarcoma 201
Anovulation 82
Anovulatory cycles, after oral contraceptives 233
— —, diagnosis of 98
— —, endometrial changes in 99, 101
— —, intermediate type 101
— —, persistent follicle 98, 100
— —, types of 99

Anovulatory cycles, with drawal bleeding of 101
Antifertility agents, see oral contraceptives,
— —, intrauterine device 247
Antigonadotropin 246
Apoplexia uteri 93, 97
Arias-Stella phenomenon, causes 136, 263
— — — in extrauterine pregnancy 282, 283
— — —, gonadotropin in 263
— — —, histochemistry of 263
— — —, in hydatidiform mole 276
— — —, incidence in abortions 263
— — — with intrauterine device 247
— — — with irregular shedding 136, 283
Arrested proliferation 221
Arrested secretion 139, 220, 221, 284
— —, focal, after intrauterine device 252
Arrhenoblastoma 146
Artefacts in curettings 18
Artefacts, histological 8
Arterioles, spiral 35, 47, 231, 237
Arteriosclerosis 93
Asherman's syndrome 256
Atrophy, cystic 84, 86
—, endometritis atrophicans 150
— from estrogen therapy 217, 243
—, from intrauterine device 247
—, from non-functioning ovaries 95, 97
— after oral contraceptives 232, 238, 243
— with ovarian tumors 146
—, postmenopausal 84, 87
—, pressure, from submucosal leiomyoma 96
— after progesterone therapy 196, 221, 238, 243
— with refractory state 97, 199, 240, 246
—, simple 84, 87
—, sterility, with 144

Basalis, characteristics of 16
β-glucuronidase 41, 239
Biopsy, techniques of 5, 6
Blastocyst, implantation of 35, 36, 48, 142
Blastomyces dermatitidis 154
Bleeding, anatomic disturbances causing 89, 92, 97
—, "breakthrough" 107, 218, 229, 231, 239
— in climacterium 145
—, estrogen withdrawal type 98, 101, 107, 218
— caused by functional disturbances 89
— in glandular-cystic hyperplasia 107
— after hormonal therapy 218
— with intrauterine devices 252
— after oral contraceptives 229, 231, 232
—, ovulatory 60
—, caused by polyps 126
—, postmenopausal 88, 150, 157, 192
—, postpartum 287, 289
—, —, and adaptation hyperplasia 288
—, caused by systemic diseases 89, 92
—, vascular causes 289 (see also menorrhagia)
—, "withdrawal" 101, 107, 118, 218, 222
Blighted ovum 259, 261, 267
Blood vessels, changes in due to relaxin 36
— — after oral contraceptives 231
Bony parts, in curettings 17, 147, 275
"Breakthrough bleeding" 107, 218
— — after gestagen 229, 231, 239
— — after oral contraceptives 218, 229, 231, 232
Brenner tumors and endometrial carcinoma 186

Candida infection 156
Capillaries, hormonal changes in 36
Carbonic anhydrase 41, 239
Carcinoma, adenosquamous 168
—, aneuploidy 118
—, associated endocrine disturbances 162, 180, 186, 191
—, — polyps 182
— and Brenner tumors 186
— in castrated patients 188
— of the cervix, differentiated from endometrial carcinoma 164, 174, 214, 215
— types 164, 214
—, chromosome studies 118, 174
—, clear-cell type 164, 166, 170
— — —, of endocervix 214
— in climacterium 145
—, constitutional factors 161, 162, 192
—, cure-rate 178, 198
—, cytoplasmic constituents of 174
—, diagnosis of 172
—, early 118–120
—, differentiation of types 164
— and estrogen therapy 186
—, etiological concepts 184, 192
— and foam cells 175, 177, 179
—, frequency 161
—, gross appearance of 10, 162, 163
—, histochemical studies of 120, 174, 198
—, histological grading 164
—, — types 164
—, hormone receptors of 197
— from hyperplasia of basalis 118, 122
—, increased estrogen levels with 184
— and liver cirrhosis 186

Carcinoma, metastases 163
—, Müllerian epithelium origin 186
—, nuclear DNA of 174, 197, 198
— and oral contraceptives 187, 237, 238
—, ovarian changes associated with 184, 186
—, after ovariectomy 189
—, pituitary disturbances in 191
—, preceding hyperplasia 117, 178, 182
—, precursors 178, 190
—, problems in diagnosis 171, 172
—, progesterone therapy for 195
—, prognosis 178
—, prophylaxis against 199
—, risk factors for 162, 180, 187
—, in senile patients 171, 172
—, sites of predilection 4, 163
— in situ, (see adenocarcinoma in situ) 179, 181
—, squamous cell 168
—, stages of 163
—, statistical studies of 161, 179
—, stroma of 175
—, stromal hyperplasia of ovary 184
—, suction biopsy of 6
—, therapy of 195, 199
—, in young women 162, 172
— after X-ray therapy 188
Carcinosarcoma 206
Cataloguing specimens 20, 21
— —, system used, advantages of 20
Cell proliferation after estrogen 41
Cellular proteins, staining for 12
Cervical carcinoma 214
Cervical mucosa (see endocervical mucosa) 15
Cholesterol, staining for, with Schulz's method 14
Chondrosarcoma 201
Chorioadenoma destruens 279
Choriocarcinoma 275, 279
—, diagnosis of 281
—, trophoblasts of 280
Chorionepitheliosis 281
Chorionic villi, disturbed development of 259, 260, 267, 270
— —, hydropic change of 258, 260, 267, 269
— —, non vascularized 270
— —, regressive changes of 267, 270
— —, retained 275
— —, stages in development 257
— —, staining for 266
Chromosomes, analysis 15
— in carcinomas 174
— in normal endometrium 22
Chromosomal anomalies in abortions 260, 270
— — after oral contraceptives 260, 261
Chronic passive hyperemia 92
Ciliated cells of glandular epithelium 24
Circulatory disorders 89
— disturbances causing uterine bleeding 90
"Clear cells" of endometrial carcinoma 164, 166
— — in hyperplasia 105
— —, types 24, 25
Climacterium 82, 86, 144
—, treatment of symptoms 199, 219
Clinical report, importance in diagnosing abnormal cycles 141
— —, — — of irregular shedding 138
— —, — of for pathologist 3
Clomiphene, therapy with 198, 217, 228, 244
Coagulation disturbances 89
Collagen inclusions 75, 263
— —, demonstration of 12, 263
— — in extrauterine pregnancy 263, 283
— —, origin 263
Collision-tumor 206
Combination-tumor 205
Compacta, beginning dissociation of 77
— of functionalis 71
—, predecidual reaction of 66, 69, 72
Composition-tumor 205
Connective tissue, formed by stromal cells 26
— —, Goldner stain for 12
— —, reticulum fibers 12
— —, special stains for 11, 12
Contaminants of curettings 18
Contraceptive agents, intrauterine device 247–254
—, Copper "T" devices 248, 251–253
— —, see oral contraceptives 224
Corpus luteum, persistent, causes of 134
— —, premature regression of 129
Cryostat, use of 7
Cryosurgery 256
Cryptococcus glabratus 154
Curettage, in abnormal bleeding 2, 145
— for anovulatory cycle 99
— for carcinoma 5
—, complete 5
—, complications of 256
—, endocervical 4, 146
—, guide lines for 3
— for hydatidiform mole 5
— in hypomenorrhea 3
— for incomplete abortion 5
—, indications for 1, 2

Curettage for irregular shedding 3
—, postpartum 287
—, precedures for 4
—, regeneration after 255
—, selection of proper time for 2
— for sterility 141, 143
— by suction 6
—, technique of 4, 5
—, in tuberculosis 152
—, value of repeated 141
— for various conditions 3
Curettings, in abortion 17, 257
—, artefacts of 18, 19
—, bony parts in 17, 147, 275
—, carcinoma of cervix in 214
—, choriocarcinoma in 275, 279
—, components of 15, 18, 214, 287
—, contamination of 18
—, diagnosis of hyperplasia of basalis 14
—, — of leiomyoma from 17, 84, 129
—, — of pregnancy 257, 266, 273, 281
—, diseases diagnosed from 89
—, extensive necrosis of causes 17, 147
— of extrauterine pregnancy 281
—, histological diagnoses of 19, 20
—, myometrial component 16, 287
—, pathological changes in 90
—, products of conception 17, 281, 284
—, re-orientation of, for sectioning 10
Cystadenofibroma 160
Cystomas of ovary 145
Cytomegalovirus endometritis 157
Cytometry 15
Cytotrophoblast 257

Dating the endometrium 15, 51, 60, 80
— —, problems after oral contraceptives 232, 240
— —, selection of criteria for 52, 60
— — in sterility 141
Decidua, of abortions 261, 263
—, after death of fetus 282
—, development of 27, 49, 258
— of extrauterine pregnancy 281
—, ground substance 259
—, hyaline remnants distinguished from hyaline thrombi 18, 272
— with intrauterine device 247–251, 284
—, involving after abortion 75, 261, 263
—, mens II 75
—, PAS stain for 11
— due to persistent corpora lutea 139
— without pregnancy 283
— after progesterone therapy 139, 221, 222, 228, 239
—, remnants of 10, 272
—, retained products of conception 17
—, reticulum fibers of 31, 282
Decidual cast 139
— — after oral contraceptives 229
— cells 29, 49, 258
— —, collagen inclusions of 263, 283
— change with ovarian tumors 145–146
—, necroses of 259
Dehydrogenases 41
— in carcinoma 175
—, after hormones 239
Delayed ovulation 143, 260
Desoxyribonucleic acid, of carcinomas 174
— — in functional diagnosis 12, 22
— — in hyperplasias 119
— — during menstrual cycle 22
— — of stromal cells 26, 27
Diagnosis of functional changes 46, 51, 82, 141, 240
Dysmenorrhea membranacea 139, 229

Edema, mechanical causes of 92
—, patchy, after oral contraceptives 90, 91, 210
—, stromal, pathologic 85, 90, 91
—, —, physiological 55, 57, 66, 68
Embedding techniques 9
Endocervical mucosa 16, 244
— —, functional disturbances of 146
— —, after contraceptive agents 242, 245
—, polyps 128
Endocervicitis 159
—, postabortum 274
Endocrine disturbances, and carcinoma 162, 180, 191
— — and endometrial hyperplasias 180, 184, 190
Endocrinopathies 89
Endolymphatic stromatosis 204
Endometrial atrophy 84
(see atrophy)
— biopsy, suction-biopsy 6
— —, technique of 5
— cytology 7
— granulocytes 71, 72, 75
— —, action of, during implantation 35, 36, 49
— — action on blood vessels 231
— — among predecidual cells 72
— —, characteristics of 27
— —, differentiation from leukocytes 13, 27, 30, 73, 147, 259
Endometrial granulocytes, enzyme contents of 40
— —, fibrinolytic enzymes in 40
— —, formation of 27, 47, 48, 66
— — at implantation site 30, 35, 49

Endometrial granulocytes at menstruation 75
— —, staining for 13, 75
— involution, first signs of 71
— stromal sarcoma 199, 204
—, stromatoses 204 (see also sarcoma)
— tissue, preparation of 7
Endometriosis, gestagen therapy for 222
—, stromal 203
Endometritis, acute 147
— atrophicans 150
—, caused by polyps 126
—, causes of 147
—, causing sterility 144
—, chronic 149
—, criteria of 147, 149
—, cyclic changes in 149
—, diagnosis of 147
— due to actinomycosis 156
— due to blastomyces 154
— due to candida 156
— due to cryptococcus 154
— due to cytomegalovirus 157
— due to herpes simplex virus 156
— due to mycoplasma 154, 244
— due to schistosomiasis 156
— due to toxoplasmosis 156
— due to viruses 156
—, foreign body granuloma 157
—, "glandularis hypertrophica" 146
—, gonorrheal 154
—, granulomatous 154
—, healing of 149
—, histology of 147
—, incidence 147, 149
—, interstitial 146
— from intrauterine device 158
—, menstrual cycle and 147
—, plasma cells in 149
—, pneumococcal 156
—, pneumopolycystic 157
—, polypoid 146
— post abortum 147, 264, 272
—, postmenopausal 149
—, postpartum 286, 287
—, regeneration of endometrium in 149
—, sarcoidosis 154, 155
—, senile 150
—, specific, due to rare microorganisms 154, 156
—, syncytial 276
— tuberculous, complications of 153
—, —, demonstration of bacteria 151
—, —, diagnosis of 151
—, —, incidence 151
—, —, sterility in 144, 154
—, —, symptoms of 144, 154
—, viral 156
Endometrium, adenoma 160
—, adhesions of 256
—, arteriosclerosis of 93
—, carcinoma (see carcinoma) 161
—, changes seen in amenorrhea 91
—, — associated with persistent follicle 98
—, — in, causing sterility 132, 141
— in the climacterium 82, 86, 144
—, cystic atrophy 84
—, dating of 15, 46, 51, 60, 80 (see dating of endometrium)
— during implantation 35, 36, 49
—, during menstrual cycle 50
—, effects of hormones on 41, 46, 223, 231
—, endocrine function of 27, 115
—, estrogen production in 115
—, extensive necrosis of 17
—, fetal 50
—, fibrinolytic activity of 40
—, foreign tissues in 275
—, functional disturbances 94
—, functionaless phase 95, 150
—, glial tissues in 275
—, histiocytes of 31
—, hyperplasia, histological characteristics 103, 104 (see hyperplasias)
—, iatrogenic changes of 216, 225
—, layers of 15, 58
—, lymphocytes of 30
— after the menopause 82
—, after menstruation 75, 81
—, methods of obtaining, preparing and interpreting 1
—, morphometry of 15
—, neoplasms 159, 210 (see specific tumors)
— in newborns 50
—, normal histology 22, 50
—, — variations in 80
—, papilloma 160
—, polymorphonuclear leukocytes in 30
—, polyps of 123, 145
—, postpartum 284
—, precancerous changes 80, 114, 115, 122, 178, 190
—, pressure atrophy of 96
—, progesterone effect 47
—, proliferation 46, 53
—, pseudomelanosis of 94
— before puberty 50
—, regeneration of 255
—, regions of 15
—, resting 96

Endometrium, sarcoma 199
—, secretory hypertrophy of 140
—, simple atrophy 84
—, socalled adenoma 124, 125, 160
—, steroid receptors 15, 42, 45, 131
—, stromal hyperplasia 128
—, stromaloma 160
—, study of whole uteri 7
—, teratoma of 161, 275
—, tissue culture 7, 15
—, transitional 85
—, transplantation 256
Endothelial proliferation caused by relaxin 16, 258, 266
Enzyme-histochemistry 38
Enzymes and hormones 38, 47, 239
—, localization of 38
—, proteolytic 40, 49
Eosinophils 31
Epithelium, glandular, nuclei and nucleoli 22
—, superficial 25
Esterase 40
— in carcinoma 175
— in endometrial granulocytes 27, 28, 40
— in hyperplasias 106, 175
Estrogen, as carcinogens 192
— "-carcinoma" 187
—, causing "clear cells" 25
—, cell proliferation 43, 46
—, effects on cilia formation 25
—, — of different compounds 102, 217, 218, 219
—, — on endocervix 146
—, — on endometrium 46, 217, 223
—, — on fibrinolytic activity 40
—, — of hypoestrogenism 97
—, — on stromal cells 26, 174
—, — of unopposed 115, 184, 192
— and endometrial carcinoma 184, 192
—, evaluating effect of, on endometrium 14, 50
— and genetic disposition 192
—, glandular-cystic hyperplasia 102, 112
—, highest levels 90
— and histamine release 46
—, hyperemia 46
—, ovarian tumors producing 145, 184, 186
—, potency 46, 217, 218
—, priming 223
—, produced by adrenals 189
—, — by endometrium 115
— receptors 42, 131
— — affinity 42, 199
— — in carcinoma 189
— receptors, clomiphene effect on 217, 246
— —, exhaustion of 217, 232, 243
—, RNA increase 23, 46, 58
—, stimulation of DNA synthesis 46, 114
—, stored in fat 191
—, stromal cells of ovary 58, 184
—, synthetic 217, 218
— therapy and endometrial carcinoma 189
— — and squamous metaplasia 110
— —, thromboses after 94
—, withdrawal bleeding 107
— withdrawal test 107, 218, 223

Fetal parts (see abortion) 17, 275
Feulgen stain 12
Fibrinolytic activity of endometrium 35, 40, 107, 108
—, — at implantation 49
— enzymes, release of 40, 49
— inhibitors 40
Fibroleiomyosarcoma 203
Fixatives 7
—, coagulants, non-coagulants 8
—, mixtures of 9
Foam cells, in adenomatous hyperplasia 114, 117, 175, 190, 194
— —, autofluorescence of 114, 118
— — in carcinoma 175, 179, 189
— — after estrogen therapy 26, 190, 219
— — in polyps 115, 128
— —, staining for 14, 114
— — from stromal cells 26
Foreign bodies, in curettings 18
Foreign body granuloma 157
Formalin fixation, advantages of 8
Frozen sections 7
— —, advantages 7
— —, selection of tissue for 10
Functional abnormalities, iatrogenic 216, 240
— bleeding, treatment of 224
— diagnosis, importance of DNA in 12
— disturbances 80, 89
— —, definition 144–145
— — during climateric 144
— —, in endocervix 146
— — in endometrititis 150
— —, in sterility 143
— —, importance of enzyme-histochemistry 38
— —, statistical analysis of 20, 21
— — in tuberculous endometritis 151
Functionalis, diagnostic value of 15
—, division of, into compacta and spongiosa 64

Functionalis, division of into layers, failure of 82
—, reticulum fibers of 31

Galactosidase 41
Gestagens, effects of 219, 221
—, —, on blastocyst 239
—, —, on endocervix 244, 245
— potency 219, 231
—, predecidual change 228
—, sarcomas after 204, 236
—, use in carcinoma 195, 222
—, use in endometriosis 224
Glands, changes in, after oral contraceptives 226, 230, 234
—, cystic dilatation of 82, 83, 84
—, — — of, with anovulatory cycles 102
—, discordant development of 130, 131
—, normal variations in 82–84
—, secretion of 24, 58, 62
— without secretory activity 82
—, tortuosity of 55, 56, 57, 60, 61
Glandular cells, changes in, during secretory phase 60
— —, ciliated cells, "clear cells" 24
— —, cytoplasm of 23
— —, nuclei of 22
— —, pseudostratified during late proliferative phase 52, 56, 57
— —, secretion of 24
— —, secretory vacuoles of 60, 62
— -cystic hyperplasia (see also hyperplasia, glandular cystic) 105
— hyperplasia 144
Glial tissue 275
Glucosaminidase 41
Glucose-6-Phosphatase 40, 41
Glycogen phosphorylase 41
Glycogen synthetase 41
Glycogen vacuoles 8, 11, 58
— —, disappearance of 62
— —, early secretion of 23, 25, 60, 62
— —, fluorochromation of 14, 58
— — after oral contraceptives 228
— —, PAS reaction for 11, 58
— —, post-ovulatory 60
— —, third day post ovulation 62
Goldner stain, advantages of 12
Gonadotropins, in abortion 262
— with Arias-Stella phenomenon 136, 263
— in choriocarcinoma 281
— after contraceptive agents 241
—, with hydatidiform mole 276, 279
—, with decidual change 284
—, reduced secretion of 241
—, therapy with 244

Granulocytes, differentiated from leukocytes 13, 27, 30, 73, 147, 259 (see endometrial granulocytes)
Granuloma, foreign body, talcum 157
—, mucus 127
—, sarcoidosis 154
—, tuberculous 151
Granulosa-cell tumor 145, 184
Ground substance, of decidua 259
—, during implantation 49
—, of menstrual cycle 35
Gynandroblastoma 146

Hemangioendothelioma 201
Hemangioma 160
Hematometra 94, 256
Herpes virus infection 156
Hilar-cell hyperplasia, ovarian 186
Histiocytes of endometrium 31
Histiocytic storage disease 254, 255
Histochemical reactions, advantages of 9, 38
Histological diagnosis, importance of clinical report 3, 19, 20
— —, correlation with clinical history and tests 4, 90, 243
— —, factors limiting 19
— —, reporting of 19
— —, statistical analysis of 20
— techniques, embedding 9
— —, fixation 7
— —, orientation of tissue 10
— —, staining 11
Hofbauer cells 271
Hormonal disturbances 94
— imbalance, detection of, by histological studies 53, 225
—, preparations 224, 226, 232
— stimuli, local unresponsiveness to 82, 96, 243
Hormone therapy for castrates 223
Hormones, changes induced in endometrium by 41, 199, 223, 243
— and enzymes 38–41
Hyaline thrombi of glandular-cystic hyperplasia 18, 107, 108, 272
Hydatidiform change 262, 267, 268, 269
— mole 260, 275
— —, and choriocarcinoma 279
— —, complete 276, 278
— — —, curettage of 5
— —, gonadotropin by 276, 279
— — —, histological characteristics of 268, 276
— —, invasive 279
— —, malignant transformation of 278
— —, partial 276, 278

Hydatidiform mole, partial, prognosis of 276
— —, transitional 267
— —, trophoblast of 268, 276, 279
Hydropic change of villi, cause of 260–263, 267
Hydroxysteroid dehydrogenases 41
Hyperestrogenism, duration of
— and endometrial carcinoma 184, 189, 190, 192
—, foam cells in 175, 189, 194
—, glandular-cystic hyperplasia 102, 112
—, importance of 112, 113, 184, 189
Hypermenorrhea 144
Hyperplasia, active 21, 95, 113
—, "adaptation" 272, 283, 289
— —, causing postpartum bleeding 289
— —, in extrauterine pregnancy 283
—, adenomatous 114, 193
— —, fate of 117, 181, 193
—, precursor of carcinoma 117, 180, 193
—, associated with carcinoma 180, 181, 194
—, — endocrine disturbances 190, 191
— of basalis 116, 122, 123
—, — —, causing sterility 144
—, diagnosis in curettings 123
—, electron-microscopic studies 106
—, focal 123
—, glandular-cystic 102
—, — —, in animals 102
—, — —, associated with persistent follicle 102
—, glandular-cystic, bleeding in 107
—, —, —, causes of 98, 102, 180, 193
—, — —, of cervix 128, 244
—, — —, changes in, after therapy 110
—, — —, "clear cells" of 24, 105
—, — —, in climacterium 145
—, — —, "discharged" 108
—, — —, after estrogen therapy 102, 112
—, — —, gross appearance of 10, 103, 104
—, — —, histochemical characteristics of 105, 106
—, — —, histology of 103
—, — —, homologous 103
—, — —, hyaline thrombi and necroses 17, 94, 107, 108, 272
—, — —, incidence 102, 113
—, — —, with ovarian tumors 145
—, — —, polypoid changes of 123
—, — —, — endometritis 146
—, — —, as precursor of adenomatous hyperplasia 112
—, — —, as precursor of carcinoma 179, 182, 190
—, — —, oral contraceptives and 234, 238
—, — —, recurrence of 110
—, — —, secretory changes in 110
—, — —, special forms 113, 123
—, — —, squamous metaplasia in 110, 112
—, — —, thromboses in 94, 107
—, — —, and tuberculous endometritis 153
—, heterologous 103
—, histochemical studies 175
— with intrauterine device 248
—, polypoid 123, 124
—, regressive 86, 113
—, resting 113
— of stroma 103, 128, 237
—, types of 103
Hypomenorrhea and endometrial atrophy 97

Iatrogenic changes of endothelium 216, 231, 232
Ichthyosis uteri 150, 169
— —, carcinomas from 169
Implantation, biochemical changes of endometrium during 49, 142
—, changes in ground substance during 35, 259
—, disturbance of 261
—, polypoid 261
—, relaxin effect during 35, 36, 48
Infarct 92
Infections, causing sterility 144
(see also endometritis)
Innervation of endometrium 38
Intrauterine adhesions 256
Intrauterine device, action of 247, 248
— —, complications of 252, 275
— —, endometritis 158, 248
— —, histological reaction to 158, 247
— —, inert types 247
— —, medicated types 248, 251
— —, pregnancy rates with 250, 251
— —, types of 248
— instillation 158, 254
Invasive mole 279
Irregular cycles 82
— shedding 134
— —, advanced 136
— —, with Arias-Stella phenomenon 136, 263, 283
— —, associated with hypomenorrhea 98
— —, causes of 134, 137, 138, 282
— —, demonstration of reticulum fibers 12, 135–138, 282
— —, diagnosis of 135, 138
— —, dysmenorrhea membranacea 139

Irregular shedding, granulocytes in 137
— —, histological characteristics 135
— —, lack of relaxin 136
— —, mechanisms in 136, 137
— —, occurrence of 134, 282
— —, oral contraceptives 138, 240
— —, post partum 289
— —, therapy for 138
Ischemia in menstruation, causes for 75
Isthmic endometrium 16

Jet washings 6
Juvenile cervical polyp 128

Karyometry 15

Leiomyoma, submucosal 96
— —, in curettings, distinguished from myometrium 17, 129
Leiomyosarcoma 201
Leukemic infiltration 201
Lipids in glandular epithelium 24, 175
—, staining for 13
— in stromal cells 13, 26, 114, 117, 175, 190
Listeriosis 264
Luteoma 145
Lymphatics 37
—, cysts 92
Lymphocytes of endometrium 30 (see also endometritis, chronic)
Lymphoid follicles 30, 32
Lymphoma 160
Lymphosarcoma 201
Lysosomes, effect of progesterone on 28, 39, 48

Malakoplakia 157
Malignant mixed tumors 201, 204, 205
—, mesenchymal 201
—, mesodermal 204
Mast cells 30
"Matron's adenoma" 125
Menopause, definition 84
Menorrhagia, due to extragenital disease 89, 93
— in glandular-cystic hyperplasia 107, 108
— from malakoplakia 157
— postpartum 287
— from talcum granulomata 158
Menstrual cycle, abnormal duration 142
— —, asynchronous 142
— —, changes of glandular cells during 22
— —, — in ground substance 35
— —, — of stromal cells during 26
— —, fifteenth day 60
— —, sixteenth day 60, 61
— —, seventeenth day 62, 63
— —, eighteenth day 62, 64
— —, nineteenth day 62
— —, twentieth day 62, 66
— —, twenty-first day 67
— —, twenty-second day 64, 68
— —, twenty-third day 66, 69
— —, twenty-fourth day 66, 70, 75
— —, twenty-fifth day 71, 72
— —, twenty-sixth day 71, 73
— —, twenty-seventh day 71, 76
— —, twenty-eighth day 71, 77
— —, irregular 82
— —, normal variations in 60, 80
— —, phases of 53
— —, its variations 50, 58, 80, 142
Menstruation cause of 73
—, early leukocytic infiltration 30
—, first day of 73, 78
— with irregular shedding 134
—, ischemia in 75
—, lack of, with normal ovarian function 97
—, processes of 75
—, release of relaxin 43, 75
—, second day of 73, 79
Metachromasia, of glandular secretion 24
— of ground substance 35
Metachromatic cells 30
Metaplasia, squamous, in adenoacanthoma 168, 169
—, —, in atrophic endometrium 150
—, —, after contraceptive agents 236
—, —, in hyperplastic endometrium 110, 112
Metastatic tumors 210
Metrorrhagia 89
Microvilli of glandular cells 24
Minipill 225
Mitoses, induced by estrogen 46
Mucoepidermoid carcinoma 164, 168, 178
Mucopolysaccharides 13, 14, 23, 35, 47, 174
Mucus granuloma 127
Müllerian adenosarcoma 204, 210
Mycoplasma 154, 264
Myelogenous leukemia 201

Necrosis, in curettings 17, 94, 107, 108, 147
—, hemorrhagic 101, 107, 108, 231
Neoplasms, benign 159
—, carcinoma (see under carcinoma) 162
—, leiomyoma 96, 129

Neoplasms, malignant mixed mesenchymal tumor 201
—, metastatic 210
—, ovarian 145
—, sarcomas 199
Nerves of endometrium 38
Neurofibroma 160
Nidation, changes in endometrium during 48, 49 (see also implantation)
Nuclei of glandular cells 22
Nucleic acids, demonstration of 12
Nucleoli of glandular cells 23
Nucleolar channel-system 23, 47, 131, 228, 238

Oocytes, abnormal, effect of 129
Oral contraceptives 224
— —, effect on ovaries 242
— —, causing irregular shedding 134, 138, 240
— —, — pathologic edema 92, 228
— —, chromosomal damage from 260
— —, combination agents 224, 226
— —, effect on endocervix 242
— —, effect on endometrial blood vessels 231
— — —, reticulum fibers 11, 230, 241
— —, effects on endometrium 225, 241
— —, — after prolonged use 232, 237, 240
— —, electron-microscopic studies after 228
— —, enzyme-histochemical studies 239
— —, functions of 224, 225, 241
— —, injectable long-acting gestagens 225
— —, late consequences 237, 275
— — and malformed blastocyst 261
— —, mode of action 240, 241
— — postcoital pills 239
— —, potency 218, 231
— —, progestagen alone 238
— —, pseudomelanosis of endometrium 94
— —, R2323 agent 239
— — resumption of fertility 240
— — sequential agents 224, 236
— —, side-effects 225, 240, 275
— —, in tissue culture 240
— —, types 224
Ovarian atrophy after contraceptive agents 241, 242
— changes, seen with endometrial carcinoma 184
— dysfunction 90, 95, 96
— function, abnormal, staining for 14
— —, changes in, detected histologically 52
— —, climacteric decline of 84, 86
— — in climacterium 144, 145
— —, effect of insufficiency on endometrium 95, 96
— —, — on reticulum network 33
— hormones 41
— — in climacterium 144
— —, control of menstrual cycle 50
— —, implantation 48
— tumors, androgen secreting 146
— —, decidual effect 146
— —, seen with endometrial carcinoma 145, 184, 186
— —, endometrial hyperplasia 145
— —, hormone-producing 145
— —, progesterone secreting 145
Ovary, hilar-cell hyperplasia of 186
—, stromal hyperplasia of 184
Ovulation, detection of 60
—, delayed 143, 260
—, premature 142
Ovulatory bleeding 60, 62
Ovum, "blighted" 259–261, 267, 269

Papilloma 160
PAS reaction, advantages of 11
Persistent follicle 98
Pessar 247
Phloxine-tartrazine stain for endometrial granulocytes 13
— — — for squamous epithelium 13
Phosphatases, staining for 38, 123
Phosphoamidase 41
Pituitary and hyperestrogenism 191
Placental polyp 275
— tissue 257, 275, 284
— — in curettings 17, 266, 274, 275
— —, necrotic 266, 269
— —, retained 5, 17, 274, 287
Plasma cells 31, 149
Plasmacytoma 201
Polyp, carcinoma arising in 116, 123, 125
—, "matron's adenoma", definition 125, 160
—, placental 275
Polyps, associated with sterility 144
— with carcinomas 182
Polyps, of endocervix, decidual change in 128
—, changes in 128
— in climacterium 145
—, clinical symptoms of 126
—, definition 123, 160
—, detection of, with van Gieson stain 11, 123
—, juvenile 128
—, occurrence of 125

Polyps of portio vaginales 128
—, sites of predilection 123, 126
— of transitional epithelium 128
— with tuberculosis 154
—, types 123–125, 160
Polysaccharides, stains for 13, 14
Postcoital pills 239
Post-menstrual regeneration 80, 81
Postmenopausal endometrium 84–86
Postpartum endometrium 284
Precancerous changes 193
— —, development from hyperplasias 193
— — in polyps 123, 125
Preclimacteric endometrium 82, 86
Predecidual cells 27, 30, 34, 47
— reaction 66, 69, 70
— — around spiral arterioles 70, 74
— —, beginning 66, 69
— —, with gestagens 228, 237
— —, with intrauterine devices 247
Pregnancy, changes in cervical epithelium during 274
—, disturbances early in 259
—, extrauterine, diagnosis of 266–275, 281–289
—, steroid receptors 45
Products of conception, see abortion 287
Progesterone, action of 44, 47, 53, 227
—, — of on mitochondria 47
—, causing pseudosarcomatous proliferation 103, 128, 237
—, effect on endometrium 219, 238, 242, 243
—, deficiency of 131
—, — on fibrinolytic activity 40
—, — on lysosomal membranes 39, 40
—, — on nucleic acids 44, 47, 197
—, — on nucleoli 23, 47, 228, 238
—, — on spiral arterioles 35, 66
—, endometrial reaction to 223, 243
—, influence on relaxin release (see relaxin) 29, 34, 36, 231
—, ovarian tumors producing 145
—, receptor 44, 49
—, secretion of, before ovulation 58
—, test 222, 244
— therapy during proliferative phase 221
— — for endometrial carcinoma 195
—, —, for endometriosis 222
— — for hyperplasias 188
— withdrawal test 218, 222
Proliferative phase, changes during 53
— —, cytoplasmic changes of glandular cells 23
— —, deficient 101
— —, early stage 53
— —, enzyme studies 38
— —, glandular cells 22–25
— —, iatrogenic 216, 225
— —, irregular 101
— —, late stage 56, 57
— —, mid stage 53
— —, stages of 53
— —, steroid receptors 45
Prostaglandins 247
Proteolytic enzymes 40
Psammoma bodies in carcinoma 177, 209
Pseudomelanosis of endometrium 94
"Pseudopregnancy" 98
Pseudosarcomatous proliferation 129, 204, 237
Pyometra 150, 152

R2323-steroid agent 239
Receptors, hormone 15, 42, 45, 131, 197
Regenerative phase, post-menstrual 80, 81
Regions of endometrium, diagnostic value of 15
Registry of diagnoses 20, 21, 240
Regressive hyperplasia 88, 103
Relaxin, absence of, in dysmenorrhea membranacea 139
—, — of, in irregular shedding 136
—, actions of 28–30, 32, 34, 47, 48
—, chemistry of 48
—, effect on blood vessels 35, 36, 48
—, — during implantation 30, 34, 36
—, — of, on endometrium 28
— in endometrial granulocytes 28, 48
—, experimental studies with 36, 37, 47
—, fibrinolytic activity of 40, 49
—, formation of 48
—, at menstruation 75
— secretion, dependent on progesterone 28, 29, 36, 48, 75
— in trophoblasts 289 (see also implantation)
Reserve cell hyperplasia, of endocervical glands 128, 146, 245
Resting endometrium 95
Reticulum fibers, characteristics of 31
— —, dissolution of 34, 35, 48
— —, during implantation 49
— — during menstrual cycle 33, 48
— —, formation of 33
— —, functional variations of 31
— — in irregular shedding 135–138
— —, staining for 12
— network, importance of, in functional diagnoses 35
— — after oral contraceptives 230
Retrosteroid 246
Rhabdomyosarcoma 201

Ribonucleic acid, criterion of estrogen effect 12, 14
— — during menstrual cycle 23, 57, 58, 75
— — in hyperplasia 105, 113, 114, 174, 175
— —, increase after estrogen 46

Salpingitis, causing sterility 154
—, tuberculous 151
Sarcoidosis 154
Sarcoma 199
— botryoides 128, 210
—, etiology 129, 204, 207
—, after gestagens 129, 204
—, heterologous 205
—, homologous 202, 205
— in situ 200
—, metastases 201, 209
—, and polyps 206
— and pregnancy 200
—, prognosis 201, 207
— and stromal hyperplasia 200, 204
—, types 205
Schistosomiasis 156
Secretions of glandular cells 24
Secretory endometrium, height of 80
— hypertrophy 140, 145
— —, cause 141, 145
— phase, abnormalities of, causing sterility 141–144
— —, changes in endometrium during 45, 53, 58
— — changes in stromal cells 26, 52, 53, 60, 64
— —, cytoplasmic changes of glandular cells 23, 24
— —, deficient 129, 141
— —, —, causes of 129, 227, 238
— —, —, clinical aspects of 133
— —, —, gestagen therapy of 134, 222
— —, —, histology 130
— —, —, incidence of 130
— —, —, types 130
— —, enzyme studies 38
— —, "arrested" 143, 221, 222, 284
— —, glandular cells 23, 24
— —, iatrogenic 226, 238, 247
— —, lipids of 24
— —, pre-implantation 48, 49
— —, socalled leukocytic infiltration of 13, 30, 73, 147, 259
— —, steroid receptors 45
Senile atrophy 84, 86
Sequential agents, see oral contraceptives 237
"Silent ovulation" 95
Sinusoidal capillaries of decidua 36, 258, 266
Spiral arterioles, changes during implantation 36, 49
— —, — in, during secretory phase 66
— —, characteristics of 35
— — in menstruation 75
Squamous-cell carcinoma 168
Squamous cell metaplasia of endometrium 110, 112
— — —, of adenoacanthoma 111, 167, 168
— — —, of endocervix 128, 244
— — —, after hormone therapy 236
Staining, advantages of special methods 11
—, aldehyde-fuchsin reaction for polysaccharides 13
— for cellular proteins 12, 13
—, complicated enzyme-histochemical techniques 14, 15
—, Feulgen stain 12
—, fluorochromation 14
—, gallocyanin-chromalum method 12
—, van Gieson method 11
—, Goldner stain 12
—, Gomori method 12
— for lipids with Sudan black 14
—, Masson-trichrome 12
—, methyl green-pyronin stain 12
—, PAS reaction 11
—, phloxine-tartrazine of Lendrum 13, 75
— for phosphatides 14
—, polysaccharides 13, 14
—, tetrazonium reaction 12
—, thionine-"enclosure" 25
Statistical analysis of histological diagnoses 20
Stein-Leventhal syndrome and carcinoma 186
Sterility from adhesions 256
—, anovulatory cycles 98, 143
—, atrophy with 144
—, causes of 144
—, —, curettage in 141
—, endometrial, disturbances in 141, 143
—, histochemical changes in endometrium 143
—, polyps with 144
— from tuberculous endometritis 144, 154
Steroid hormones 41
—, — molecular biology of 42
—, — receptors for 15, 42, 45
Stromal cells, changes in, during menstrual cycle 26, 64
— —, — in, during proliferative phase 60

Stromal cells, changes in, during secretory phase 60, 64
— —, characteristics of, in normal endometrium 26, 27, 30
— —, differentiation of 26, 27, 67
— —, enzyme systems of 27, 239
— changes after oral contraceptives 217, 220, 221, 228, 230, 236, 237
— edema after oral contraceptives 90, 91, 210, 228, 237
— —, pathologic 90, 92
— endometriosis 203, 222
— hyperplasia 103, 128, 160, 200, 204
— —, nodular 204, 236
— — and sarcoma 128, 200, 202, 237
— sarcoma 199, 204
—, homologous 201, 202, 205, 207
—, polymorphic 200
Stromaloma 160
Stromatoses 204
Suction-biopsy, limitations of 6
Sudan black stain 14
Superficial epithelium, characteristics of 25
Syncytial endometritis 276
Syncytiotrophoblasts 257, 267, 276, 280
Systemic diseases, causing uterine bleeding 89, 92

Tachyphylaxis 43
Talcum granuloma 157
Tamoxifen 44, 197
Target organs 42
Teratoma 161
Theca cells, characteristics of 185
Thecoma 145
Three sequence preparations 225
Thrombotic thrombocytopenia of the endometrium 93
Thromboses 94, 253
Tissue culture of endometrium 7, 15, 197, 240
Toxoplasmosis 156, 266
Trophoblasts 260, 261, 266, 267
—, abnormalities of 270
—, action on vessels 289
—, of blighted ova 268
—, with decidua 266
—, of hydatidiform male 269, 276, 279
—, retained 272, 275, 287, 289
Tuberculosis 144, 151
Tumors, metastatic 210
—, ovarian 135, 145, 184, 186
—, sarcomas 199

Uterine bleeding, atypical 89 (see also bleeding)
— — due to extragenital diseases 89, 92

Vacuum aspiration 6
Van Gieson stain, advantages of 11
Veins, hormonal changes in 36
Vessels of endometrium 35
Villi, see chorionic villi 257, 261, 266

Withdrawal bleeding, cause of 98, 101, 107
— —, estrogen 218, 223
— — in glandular-cystic hyperplasia causes of 107
— —, progesterone 218, 222, 231

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