Gynecologic Oncology

FUNDAMENTAL PRINCIPLES AND CLINICAL PRACTICE

2

EDITED BY

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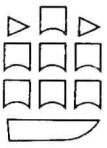

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Foreword

This treatise deals with a specialty that has come of age. And it has done so in just under fifty years, for surely among the first intimations was the publication of Meigs' classic *Tumors of the Female Pelvic Organs* in 1934. It is notable that one man in that year could write a book based on one hospital's experience and cover the subject so completely that the resultant text served us well for over a decade. Whereas now the multidisciplinary nature of the subject, in all its scientific and clinical ramifications, must call upon a host of authors and many institutions if the editor truly seeks to spread before us the best and latest word on every relevant facet.

It is not mere chance that this specialty within a specialty evolved in gynecology. Most pelvic cancer in the female is accessible and treatable, and some gynecologists and pathologists have stepped forward in every decade to dedicate themselves to its study. As a consequence a series of signal advances, many of which have been applicable to oncology in general, have first been promoted in gynecologic oncology. There has been first the use of radium and X-ray for curative purposes, then the classification of disease by stages in order to be able to evaluate treatment, next the identification of a preinvasive stage of squamous cancer, then the epoch making observations of Papanicolaou in cytology, and finally the purposeful designing of curative protocols for disseminated disease by chemotherapeutic agents.

Twenty-five years ago the gynecologic oncologist was first and foremost a surgeon, often the most radically oriented technician on a hospital's roster. He was clearly not an obstetrician but his orientation and the necessity for equal facility from the perineal as well as the abdomino-pelvic approach set him apart from the general surgeon. The best among us had more than passing acquaintance with pathology, radiotherapy, and more recently with chemotherapy. Encouraged by spectacular improvements in anesthesia and the support mechanisms to control shock, sepsis and other metabolic reversals, this cohort of pelvic surgeons during the middle decades of the century systematically explored the ultimate perimeters of radicality.

Much was learned, particularly about the natural course of gynecologic cancers, but the era is ending as the data accumulate to indicate that in the main the increased salvage is small. The potentials and indications for various procedures have sorted themselves out, and a new generation of oncologists has arrived on the scene, trained in multiple disciplines and philosophically oriented to individualization of the clinical presentations and to a careful and logical selection of the optimum program for each patient.

For the gynecologic oncologist of this stripe, a book like this one is indispensible. It will be uniquely useful to those who have the specialty under contemplation, as a learning tool to trainees and a reference source for the accredited specialist. Malcolm Coppleson is to be congratulated for the muster of highly qualified contributors he has rallied, for the breadth, depth, and variety of topics dealt with, and for the time and attention he has so obviously devoted to the pursuit of excellence in an area of biological science he has himself long adorned.

Boston, 1981 H.U.

Preface

Each year the problems of oncology become more and more complex as the advance of knowledge uncovers further detail at every level of investigative endeavor from the basic through epidemiologic to the clinical and aftercare. Some of these advances are sufficiently valuable as to require a place of recognition if not actual use in the daily round of the busy practitioner and there is a persisting problem of the presentation of this intelligence in the most appropriate form consistent with the time available for its assimilation. On balance there is a good case to be made for the traditional comprehensive textbook with its properties of convenience, condensation and permanence as a persisting vehicle for this burgeoning output from the clinics and laboratories of the world. This book has been designed to fill a hiatus in the library for a comprehensive, authoritative and particularly detailed, even encyclopedic, treatment of the whole field of gynecologic oncology for an equally wide range of practitioners from the novice attempting entry into the specialty (the Boards level of American parlance) through the typical specialist to the superspecialist of to-day.

To effect this broad design I have invited a large number of distinguished authorities from leading centers in various countries, alike in the height of their repute often on a world basis, their grasp of the field often as a direct result of years of original study, and their ability to epitomize a great mass of detailed information, itself a reflection of the amount of information now generated on every conceivable topic. Each was briefed on the editorial aim of vesting the most recent views on the principles or basic framework of a given topic with a wealth of personal experience, technique and know-how to ensure the understanding and execution of these principles at the bedside or in the theater. Editorial authority for its part has been asserted frequently and intensively through the miscellany of subjects to avoid redundancy, keep the story coherent and ever instructive, even entertaining. A strict regime was established for unifying subdivision of the material of each topic to preserve a sense of coherence and regularity such as might be expected were the whole volume to be the work of one author, and to facilitate the reference function of the book. Extensive cross-referencing within the book has been an outcome of this policy.

The manipulation of such a large volume of material has focussed attention on its arrangement. The subject matter progresses from a description of the theoretical background of the specialty, through diagnosis and its techniques, to descriptions of tumors of gynecologic significance, vulva, vagina, uterus, tube, ovary and trophoblast. Each tumor type is discussed through its pathology, clinical features and treatment. The surgical aspects of treatment are given extensive coverage, not only of the more conventional operations but of the newer conservative methods which are now in widespread use for the management of intraepithelial and other very early stages, and of the new approaches to vulvar and vaginal reconstruction. There is a growing awareness of the importance of aftercare and this has been accommodated in a series of chapters following the descriptions of major complications of radical surgery and irradiation which have made the subject of aftercare so necessary.

I thank the many distinguished contributors who made this book possible for their considerate and friendly co-operation. Their efforts, complicating further their own busy daily rounds, are appreciated. It is a pleasure to express my great debt of gratitude to my friend, scientific collaborator and co-author of other books, Bevan Reid, for his continued encouragement, sound counsel and invaluable assistance in countless ways. Without his generous help the undertaking would have been more onerous. I wish to acknowledge the part played by my colleague and friend, Dr Albert Singer, for his encouragement and reassurance when the project was first mooted. I acknowledge the generous co-operation of the many authors, journals and publishers who have permitted the use of graphs, drawings, photographs and statistical material. Due acknowledgment is given to each in the text. I extend my thanks to my personal secretaries, Shirley Bottrell, who spent so many tedious hours typing much of the manuscript, and Mary O'Connor. They were gracious, ever-helpful and ever-forbearing over the many months of the project. I thank Peter Ffrench for painstaking bibliographic and other assistance. My sincere thanks are due to the staff of Churchill Livingstone, especially Sylvia Hull, Dinah Bagshaw and Andrew Stevenson, who at all stages of production have been enthusiastic, co-operative and have always displayed a deep understanding of the book's requirements.

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Premalignant lesions of the endometrium: "Endometrial hyperplasia and adenocarcinoma in situ"

W. M. Christopherson and L. A. Gray

INTRODUCTION

The term premalignant is rather imprecise and at times evasive. It has been applied to a variety of lesions that would appear to have varying degrees of potential for the subsequent development of cancer. The degree of risk is known for only a few "precancerous lesions", for example xeroderma pigmentosa and familial polyposis. Other less obvious cancer precursors such as solar keratosis and isolated colonic adenomatous polyps have a less well documented premalignant connotation.

In the female genital tract there have been several lesions which at one time or another were presumed to be premalignant but have not endured the test of time. One such example is vulvar leukoplakia. At one time it was so highly regarded as to have resulted in what presently would be considered excessive surgery. Leukoplakia currently is not even recognized as a specific pathologic entity and vulvectomy is no longer recommended for these white patches. Other lesions exist which because of their worrisome histological appearance, would seem likely to be cancer precursors. An example is the recently described Bowenoid papulosis of the vulva for which there is currently little biologic evidence of premalignancy.[50] The association of clear cell carcinoma with vaginal and cervical adenosis resulted in the postulation that adenosis was probably a precursor of clear cell carcinoma. Evidence for this has not materialized.[20] To date only one clear cell carcinoma has apparently developed in a young woman while under surveillance for vaginal adenosis.[1]

The association of hyperplasia with adenocarcinoma of the endometrium has been amply documented.[4, 8, 14, 15, 36, 46, 47] Both are associated with estrogen,[5, 10, 30, 32, 33, 39] however, proof that hyperplasia is a transition stage is more difficult to document.

The lack of uniform terminology and the impreciseness of definitions that have existed for over half a century compound the problem of understanding the predestination of endometrial hyperplasia. Prospective studies are difficult to conduct because of the lengthy follow-up required. Another obstacle to long term surveillance is that hysterectomy is often performed in the interim or the exogenous estrogens withdrawn after hyperplasia is diagnosed. The studies also lack consistency of terminology and definitions previously mentioned.[6, 9, 21, 31] The precise relative risk is thus difficult to determine from past studies. The risk, however, does seem greater for postmenopausal than for premenopausal women.[29, 37]

It is now generally agreed that invasive cancer of most, if not all, sites must evolve through an in situ stage. There is convincing biological evidence that such is the case.[44] Logic would compel us to believe that even carcinoma in situ is not likely to develop de novo but rather evolve from precursor lesions. The important point is that the many morphologically disturbing epithelial lesions have not only a wide spectrum of cytologic and morphologic changes, but undoubtedly a wide variety of initiating factors, and for some at least a similar wide spectrum of biologic potential.

There is ample evidence that both endometrial hyperplasia and carcinoma are estrogen dependent and that either endogenous estrogens in excess or unopposed exogenous estrogens predispose to their development. There appears to be an increased risk for endometrial hyperplasia as well as for carcinoma in women with estrogen producing tumors[30] and in women with sclerocystic ovaries.[25] The latter are anovulatory and thus would presumably have noncyclic estrogen stimulation of the endometrium. At the other end of the spectrum women with gonadal dysgenesis rarely develop endometrial hyperplasia or endometrial adenocarcinoma unless they receive estrogen therapy to promote secondary sexual development.[5, 10, 39] To complicate the picture, most of the estrogen-treated hypogonadal patients appear not to develop hyperplasia and in one study those that did received a life-time conjugated estrogen dose of 2500 mg or more for periods longer than 4.2 years.[39]

While it appears to be unlikely that endometrial hyperplasia or adenocarcinoma develops in the absence of estrogens, the precise role of estrogen is poorly understood. The endometrium is perhaps the most dynamic tissue in the

body. Its cyclic regeneration, maturation and shedding is dependent on the female sex hormones, notably estrogen and progesterone. In women with anovulation or irregular ovulation the persistent estrogen stimulation can produce a continuous proliferation of the endometrium that could, by pathologic definition, be considered hyperplastic. Recognizing the significance of such changes in a younger woman, most pathologists would prefer to diagnose such samples as being consistent with ovulation failure rather than reporting the change as "proliferative hyperplasia or simple hyperplasia", which in fact it is, albeit not immediately related to a premalignant change. Atypical endometrial changes are also associated with the presence of chorionic tissue.[2] This is a physiological phenomenon which is totally reversible.

Table 42.1 Precursor lesions of invasive endometrial carcinoma[a]

1. Cystic hyperplasia
2. Adenomatous hyperplasia
3. Atypical hyperplasia
4. Carcinoma in situ

[a]After F. Vellios[48]

Essentially every author who has written on the subject of endometrial hyperplasia has stressed the need for uniform terminology and for uniform definitions, usually pointing out the difficulties in determining the premalignant potential of a particular pattern due to the inconsistency of definitions. For this reason we have chosen to use the classification adopted by Vellios who is currently writing the Armed Forces Institute of Pathology (AFIP) fascicle on the uterus[49] (Table 42.1).[48] These authoritative volumes are widely used as standard references by pathologists both in the United States and abroad. We have no other *a priori* reason to select this classification. Since the diagnoses are highly subjective all definitions must be somewhat imprecise within the limits of subjectivity, however, a degree of uniformity is absolutely essential in classification if more precise knowledge of the relative significance of the various degrees of hyperplasia are to be elucidated sometime in the future.

The historical account of the lesions under discussion has been thoroughly covered by numerous authors[15, 16, 48] so it need not be repeated here. The discussion will be confined to those types of endometrial hyperplasia and carcinoma in situ that may be precursors of adenocarcinoma of the endometrium.

PATHOLOGY

Cystic hyperplasia

The least controversial type is cystic hyperplasia. It must be distinguished histologically from proliferative endometrium with the occasional cystic gland. In patients using sequential contraceptives and in the occasional anovulatory endometrium, the glands may also be dilated.[48] Cystic atrophy can acquire a polypoid configuration and should not be confused with regressing cystic hyperplasia. In cystic atrophy the glandular epithelium is flattened and atrophic and the stroma tends to be reduced in amount and often appears fibrous (Fig. 42.1).

Fig. 42.1 Cystic atrophy of the endometrium. (H & E × 79).

On gross examination endometrium in cystic hyperplasia may be increased in thickness and polypoid areas may be present. The amount of material obtained by curettage is usually more abundant than is the case in proliferative phase endometrium. Unlike carcinoma the gross specimen is soft and appears mucoid and glistening.

Under low power magnification it is characterized by dilated cystic glands whose lumens may contain debris and histiocytes. There is no particular crowding of the glands as opposed to the more marked forms of hyperplasia. The stroma often in fact appears to be increased in amount. The morphology has led to the term "Swiss cheese hyperplasia" (Fig. 42.2).

Under higher magnification the stromal cells are densely packed and their nuclear diameter is larger than the stromal cells in proliferative phase endometrium.[19] Mitoses in both stroma and glands are variable but can usually be found without much difficulty. Atypical mitoses are not encountered. The surface epithelium and the cells lining the gland lumens may be columnar, cuboidal or flattened, largely

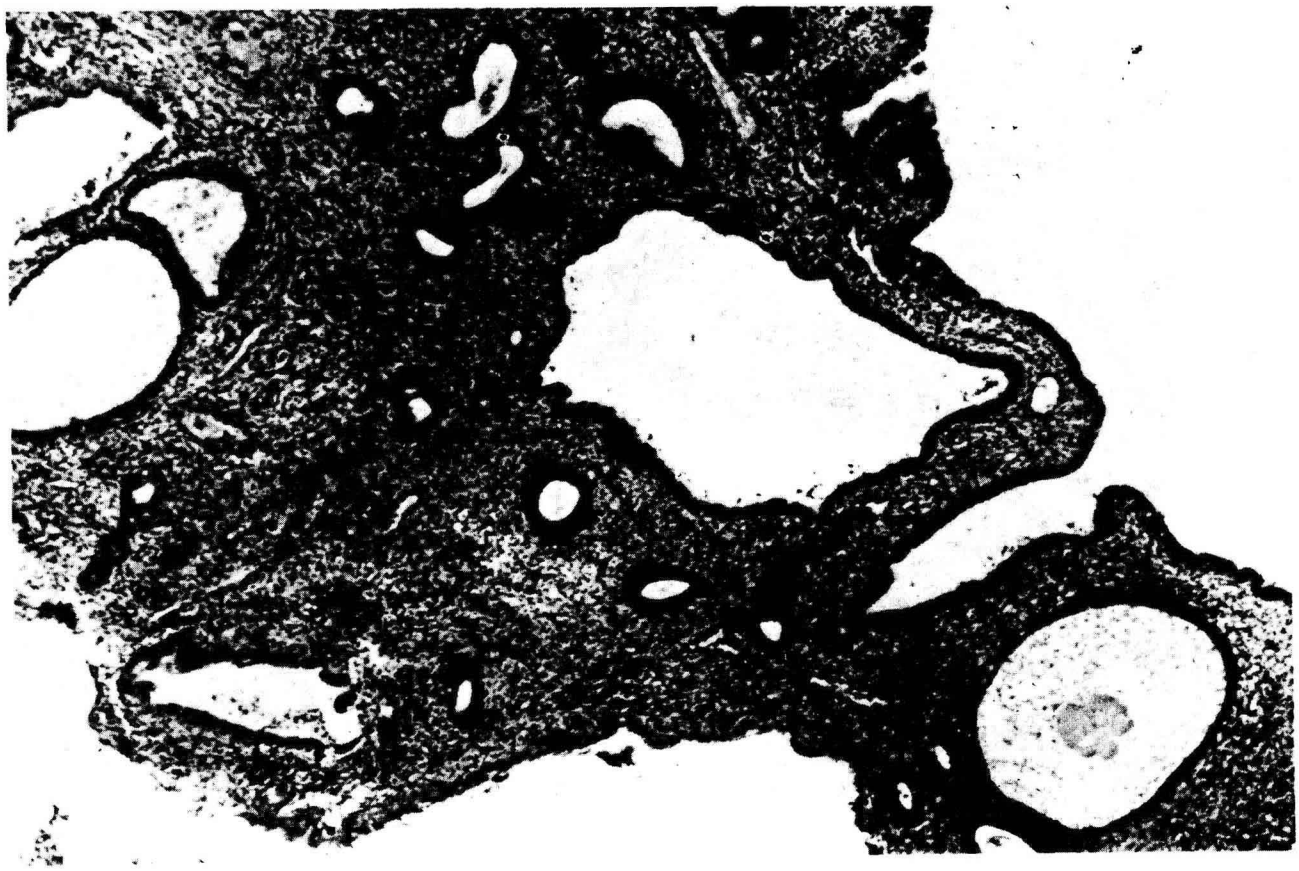

Fig. 42.2 Cystic hyperplasia from curettings. Note the abundant stroma and non-crowding of the glands. (H & E × 79).

dependent on the degree of dilatation of the particular gland examined. Pseudostratification, if present, is patchy and minimal. Well formed cilia can be found, usually in large numbers. They are usually absent in the very distended glands. The nuclei of the columnar cells are elongated, usually vesicular and are oriented perpendicular to the surface. Chromocenters may be distinct but nucleoli are not (Fig. 42.3). Chromosome analysis and microspectrophotometric patterns are said to be identical with those of nuclei of the normal proliferative endometrium.[24,51]

Adenomatous hyperplasia

This category of endometrial hyperplasia is noted by essentially all authors as an area of some confusion and disagreement, due largely to terminology and definitions. The term as used by Gusberg is a comprehensive one which also includes atypical hyperplasia and carcinoma in situ.[16,17,18] It has been modified by subsequent authors to denote more specific histologic changes.[21,48] Since the more recent trend seems to be to attempt to separate adenomatous hyperplasia from lesions which appear morphologically and cytologically more advanced, we will use the more restrictive definition.

Adenomatous hyperplasia produces an increased thickness of the endometrium either in a diffuse pattern or in an irregular fashion with the hyperplasia intermingled with normal endometrium. At times it occurs as a focal change in cystic hyperplasia, and scattered dilated cystic glands are occasionally present in predominantly adenomatous hyperplasia. The low magnification appearance is one of closely packed, irregularly distributed glands. There is glandular outpouching into the endometrial stroma and these evaginations may appear in clusters with a microfollicular pattern adjacent to the larger irregular gland (Fig. 42.4). The appearance is dependent on the plane of section. The epithelium is similar to that of proliferative endometrium. The nuclei are uniform and tend to be oval and are without prominent nucleoli. The degree of pseudostratification is usually minimal and depends largely on the thickness of the section. Mitoses are usually frequent. Squamous morules are occasionally found (Fig. 42.5). The stroma is variable and rarely the stromal cells are fat laden as they may also be in atypical hyperplasia as well as in endometrial carcinoma. When the term adenomatous hyperplasia is used in this more restrictive sense it is not easily confused with well differentiated adenocarcinoma.

Atypical hyperplasia

Atypical hyperplasia, like the other forms, usually produces a thickened endometrium which may be quite copious on the curettage specimen. It usually occurs in conjunction with one

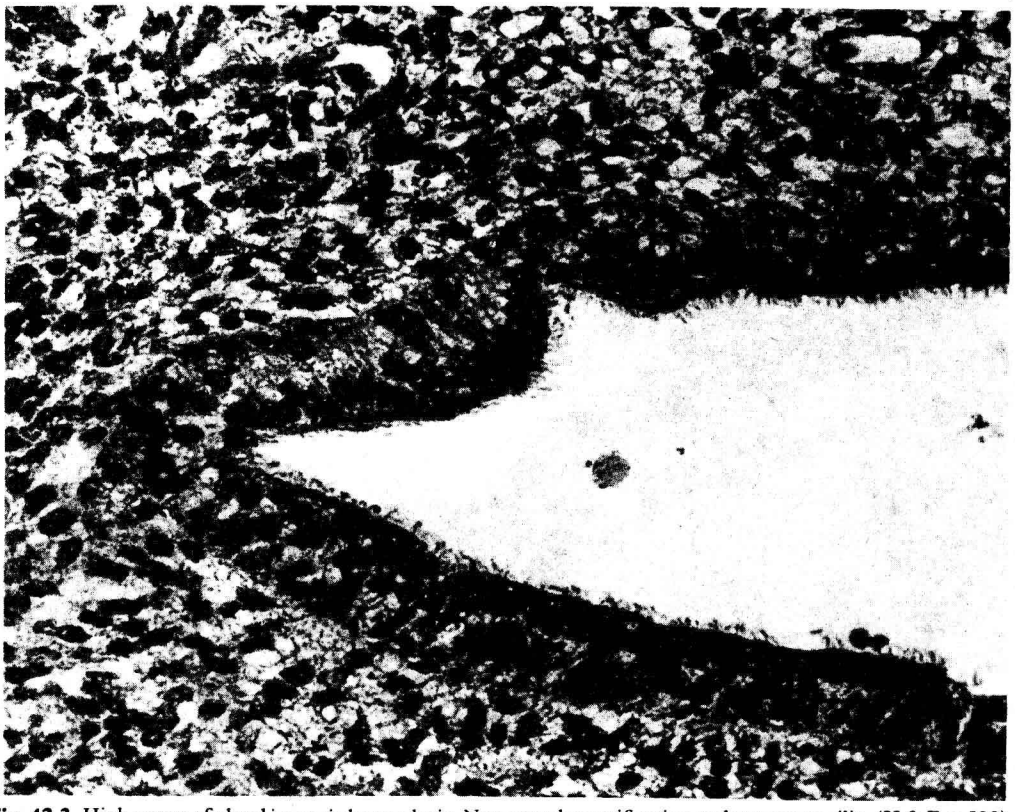

Fig. 42.3 High power of gland in cystic hyperplasia. Note pseudostratification and numerous cilia. (H & E × 500).

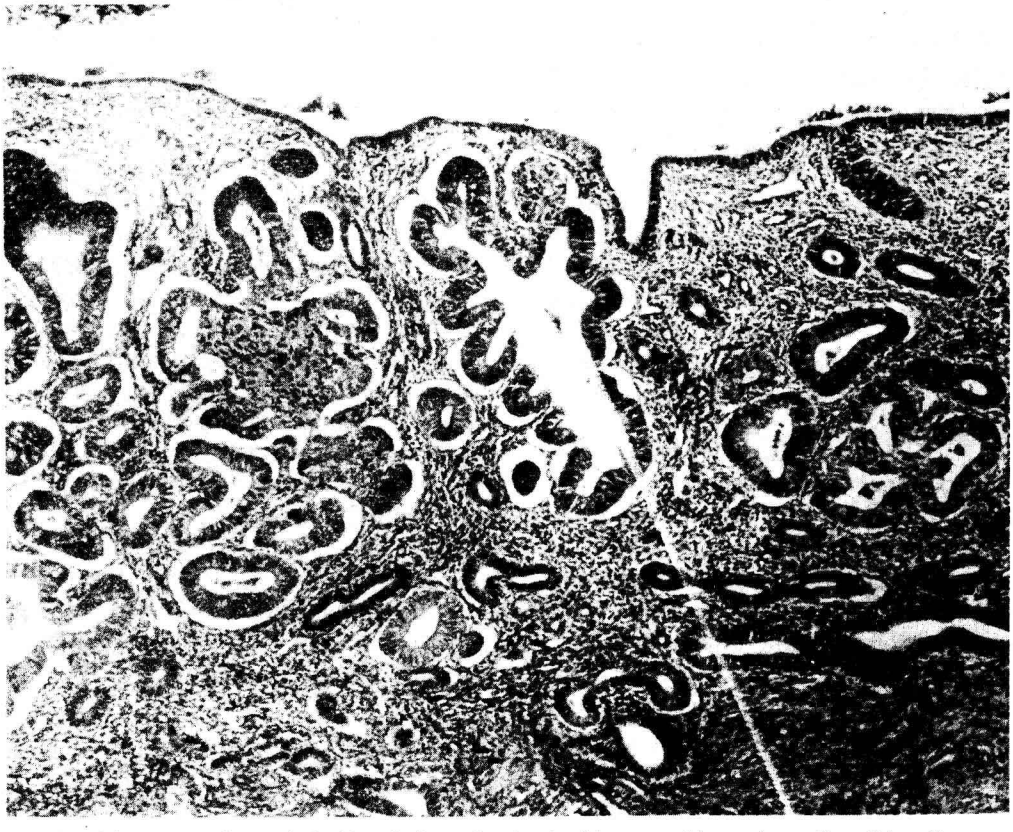

Fig. 42.4 Adenomatous hyperplasia. Note the irregular glands with outpouching and crowding of the adjacent smaller glands. There is a squamous morule to the left. (H & E × 79).

of the lesser forms of hyperplasia and is rarely diffuse throughout the entire endometrium. It is characterized by larger, very irregular glands with a pronounced decrease in the intervening stroma. The process of proliferation produces infolding into the glandular lumen. This at times may be extensive (Fig. 42.6). The definitive diagnosis depends on a critical evaluation of the epithelial cells (Fig. 42.7). The nuclei are large and tend to round out, there is nuclear pleomorphism but distinct nucleoli are not common. When they are present they are not as prominent, as irregular nor as often multiple as they are in carcinoma in situ. In contrast to carcinoma in situ the amount of cytoplasm is not greatly increased and is not eosinophilic. Both squamous morules and fat laden stromal cells may occasionally be present (Fig. 42.8).

Carcinoma in situ

Carcinoma in situ of the endometrium is perhaps the most controversial lesion under discussion. Some authors do not use the term, preferring to group such cases with adenomatous hyperplasia,[16, 17, 18] or atypical hyperplasia.[35] The lesion as defined by Hertig and associates[12, 22] and later by Buehl, et al[7] and by Vellios[48] has a distinctive histologic appearance. Using the criteria of these authors it is possible to delineate a group of endometria that can be distinguished from adenomatous and atypical hyperplasia as herein described and on the other hand from invasive endometrial carcinoma. Whether this delineation can be correlated with the malignant potential of the various lesions remains to be proven.

In a recent review Welch and Scully stressed the cytologic features and the limited extent of carcinoma in situ as important criteria for diagnosis.[52] If more than five or six glands are involved those authors designate the lesions as adenocarcinoma with the realization that invasion of the stroma is often impossible to distinguish from the crowding of noninvasive atypical glands. We are in agreement with these authors in that the cytologic features are most important, however, we are less restrictive about the extent of the lesion. The problem is quite similar to that in identifying microinvasion in adenocarcinoma in situ of the cervix. Vellios intends to use the designation focal invasive carcinoma for the more extensive, presumably more advanced lesions.[49]

Endometrial carcinoma in situ has no gross characteristics which distinguish it from other hyperplastic lesions. Histologically the most striking feature is the focal nature of the lesion in combination with hyperplasia. Curiously the change seems to accompany cystic hyperplasia as frequently as it does the more advanced types. The epithelial cells are

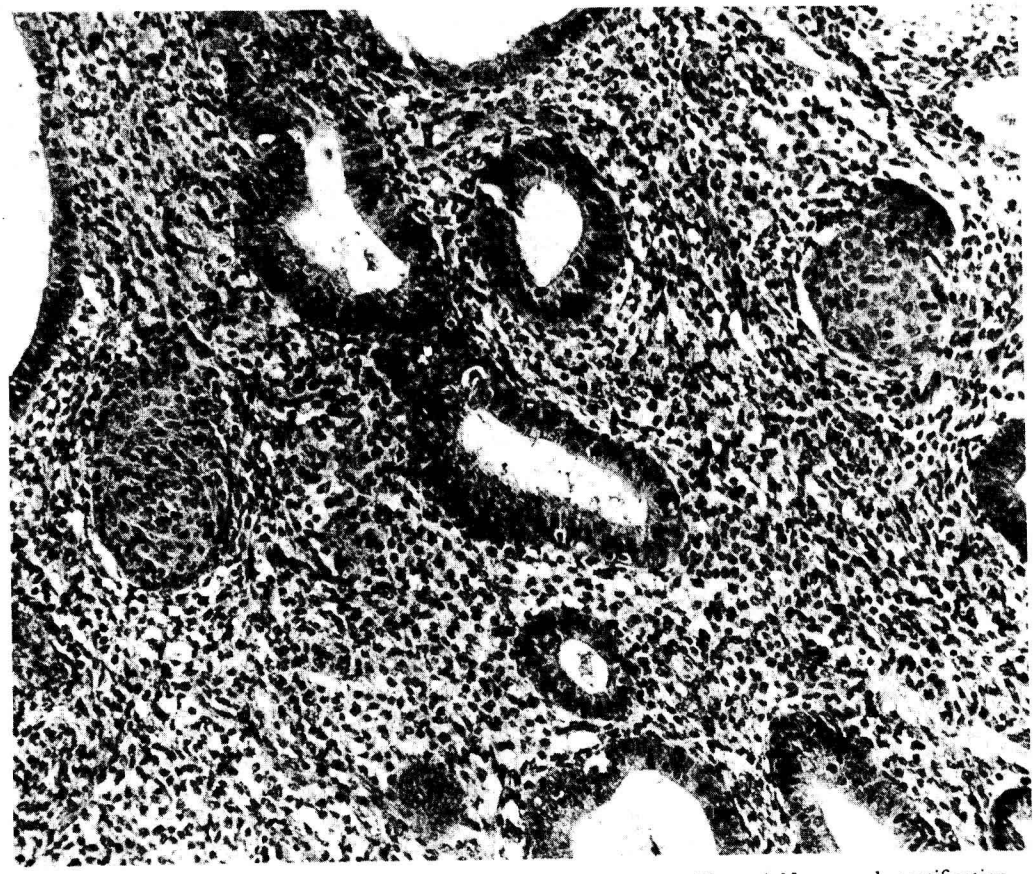

Fig. 42.5 Adenomatous hyperplasia with squamous morules. Same case as Figure 4. Note pseudostratification and numerous mitoses in the glands which are much less crowded than in Figure 4. (H & E × 197).