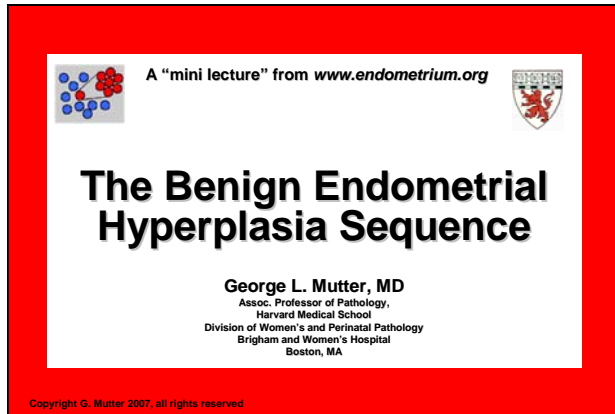


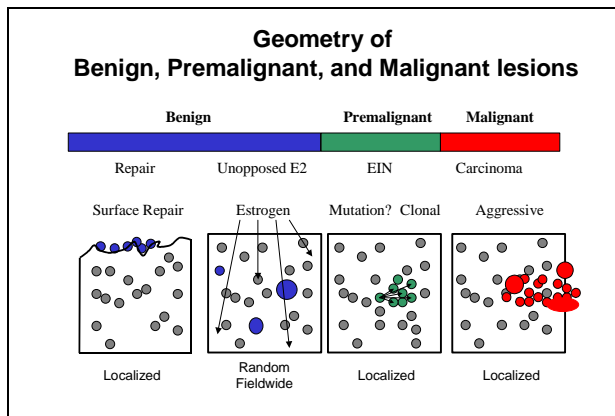
Slide 1



Introduction

This is Dr. George Mutter, I am a gynecologic pathologist at Harvard Medical School, and the Division of Women's and Perinatal Pathology at Brigham and Women's Hospital in Boston. This is a mini lecture on the endometrial effects of unopposed estrogens, which we refer to as the benign endometrial hyperplasia sequence.

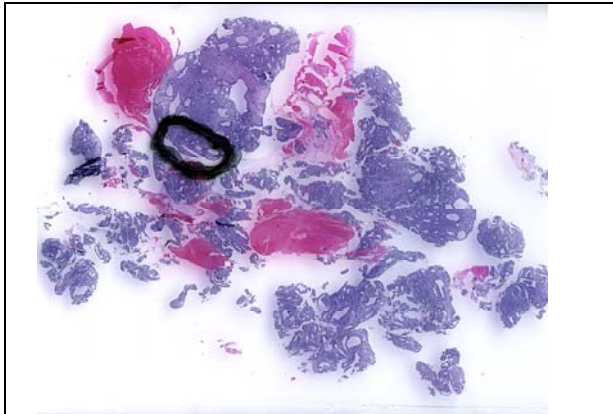
Slide 2



Diffuse Topography

In the previous lecture, we talked about how premalignant EIN lesions emerge within the endometrial field from a single point in space. This topography is explained by clonal emergence of proliferating genetically mutated cells. As time goes on, these may expand to involve the entire endometrial compartment, but most patients will only have a localizing process at the time of initial diagnosis. The endometrial effects of circulating hormones are quite different. They have access to the entire endometrial compartment, and therefore generate changes throughout. The resultant increase in glandular and stromal bulk may be properly termed *hyperplasia*. We use the term *benign endometrial hyperplasia* to describe a constellation of changes caused by unopposed estrogens. Dynamic change of the endometrial tissue during and throughout exposure creates a histologic appearance that is unique for each patient. The histologic presentation at any time point will be exquisitely determined by the tempo and level of estrogen exposure, an appearance that may be further modified by disappearance of the estrogen or superimposition of a progesterone effect. The dynamic, constantly changing character of these influences creates a sequence of alterations over time rather than a singular and static appearance.

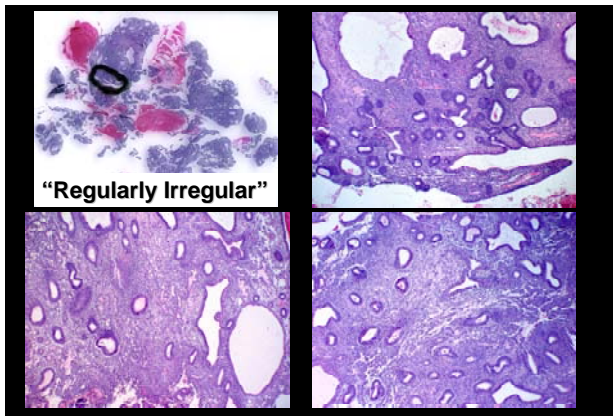
Slide 3



**Random Cysts**

Here we have lush fragments of endometrial tissue removed by curettage from a woman who was anovulatory. Protracted estrogen exposure has acted upon all fragments, creating cystic structures which are randomly distributed throughout.

Slide 4



**“Regularly Irregular”**

Under low-power magnification, there is a uniformity of involvement of all tissue fragments. This impression may not be maintained when smaller areas are magnified to a higher extent as seen in the lower and right panels of this image. At a medium-level magnification, smaller areas have very differing individual appearances. The density of cysts, and extent of crowding of glands, change from field to field. I like to call this pattern “regularly irregular”. This describes the low-power impression of a random distribution of changes as a regular pattern, but one which on closer observation looks quite different within each field. This is one of the primary characteristics of benign endometrial hyperplasia.

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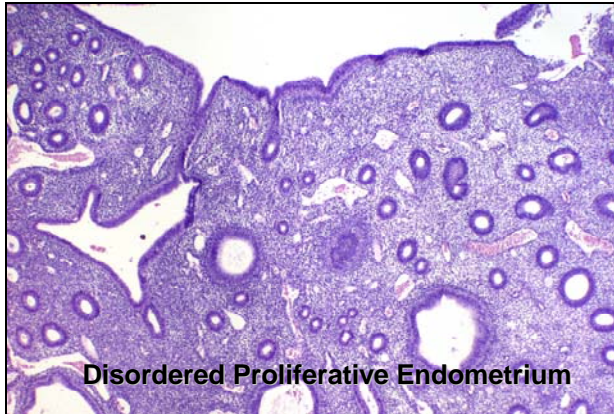
**Unopposed Estrogen**

- Proliferative
- Cysts
- “Regularly Irregular” architecture
- Tubal change scattered randomly
- Fibrin thrombi and breakdown

**Estrogen Histology**

In the presence of estrogens, glands and stroma undergo proliferation. Cysts and tubal metaplasia develop progressively in a random distribution. With even longer exposure, small blood vessels within the endometrial functionalis undergo thrombosis. Fibrin thrombi within these vessels are usually accompanied by an adjacent breakdown of the surrounding endometrial stroma.

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**Disordered Proliferative**

I would like to walk you through the sequence of changes which take place with increasing duration of estrogen exposure. Of course, the first change is induction of a normal proliferative endometrium composed of evenly-spaced tubular glands with mitotic activity. The first noticeable effect of an overly long estrogen exposure is cystic dilatation of randomly scattered glands dispersed within this regular array of pre-existing proliferative glands. The gland density is not significantly changed. Occasional glands may have some branching. The histology is usually referred to as a *disordered proliferative endometrium*. A functional synonym is *persistent proliferative endometrium*, which describes an abnormal duration of estrogen stimulation as the underlying event. A clinical term for these patients is *anovulatory*, as they lack the progesterational effects of the postovulatory corpus luteum.

Slide 7



**Benign Hyperplasia Example 1**

As time goes on, remodeling of glands and adjacent stroma takes place. Like cyst formation, this is a diffusely random process that generates varying density of glands across individual fragments. Some cysts have tubal metaplasia, as seen in this example. Establishing a boundary between disordered proliferative endometrium and benign endometrial hyperplasia is somewhat arbitrary, as the underlying process is the same, unopposed estrogens. The feature which we use to distinguish between benign endometrial hyperplasia and disordered proliferative endometrium is the presence of substantial areas of gland crowding where the gland area exceeds that of the stroma. This is usually a multi-focal process encompassing several areas of the endometrium. Importantly, the cytology of the crowded glands is similar or identical to the cytology of more widely-spaced glands elsewhere in the specimen. This feature distinguishes it from premalignant EIN lesions.

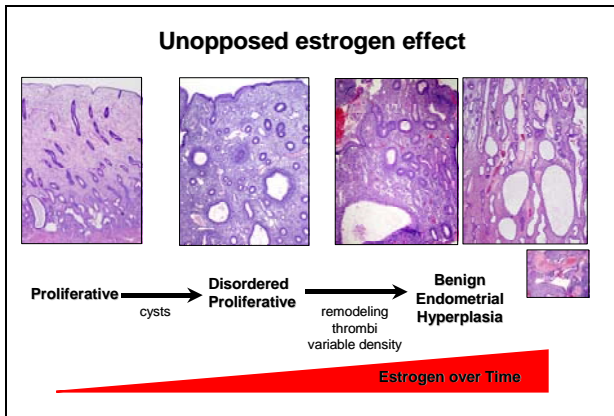
Slide 8



**Benign Hyperplasia Example 2**

Eventually, few tubular normal appearing glands remain. A combination of high gland density with cystic dilatation of other glands reduces the proportion of intervening stroma. In this example, essentially all fragments have a gland surface area which is greater than that of the intervening stroma.

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**Sequential Estrogen Effect**

This diagram summarizes the sequence of changes we have just discussed. Beginning with a proliferative endometrium, scattered cysts define a disordered proliferative pattern. When remodeling leads to a glandular area greater than that of stroma, this may be referred to as benign endometrial hyperplasia. The architecture of established benign endometrial hyperplasias is further altered by fibrin thrombi and resultant stromal breakdown. The intuitive linear sequence of progressive change is oversimplified for many patients. The duration of estrogen exposure is not the only relevant variable. The estrogen level can fluctuate, or its effects may be interrupted by a delayed ovulatory event or administration of exogenous progestins.

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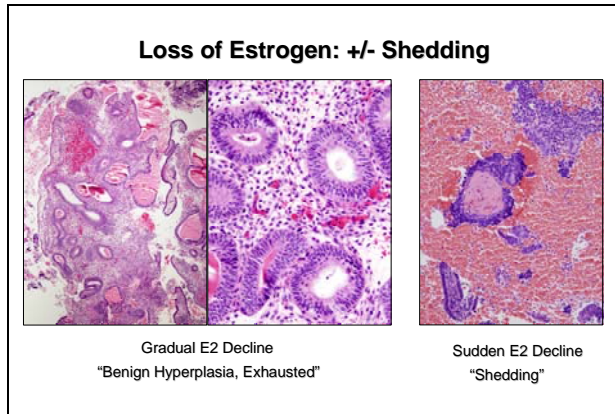
**Unopposed Estrogen Changes Can Outlast Estrogen!**

- Estrogens may be gone at time of Bx = Amitotic glands
- Breakdown and Shedding common, BUT
- Architecture May be Preserved: Spectrum from scattered cysts to Benign "Hyperplasia"
- Fibrin Thrombi visible in intact and shedding tissue

**Post-Estrogen Appearance**

Many of the histologic features of unopposed estrogens remain in the tissue even after the estrogen is no longer present. If the estrogens decline in a gradual manner, there may be no wholesale shedding of the endometrium, but rather a gradual decline in mitotic activity. In these cases, a benign endometrial hyperplasia architecture may be accompanied by amitotic glands. Some features, such as fibrin thrombi and stromal breakdown, persist for varying intervals after the estrogen has stopped.

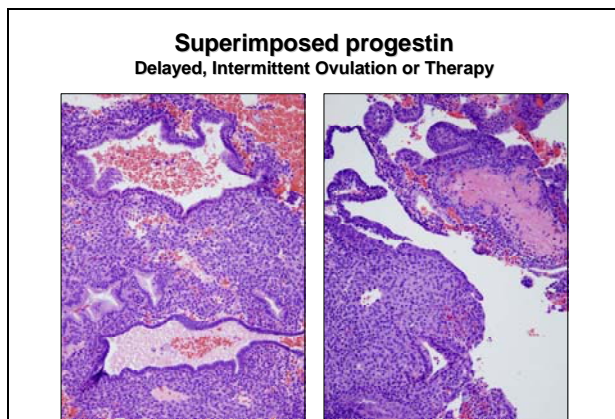
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**"To Shed or Not to Shed"**

These modifying scenarios of estrogen loss or progestin exposure increase the spectrum of endometrial histologies seen after priming by unexposed estrogens. Here you see an example of a patient with scattered cysts of a hyperplastic endometrium. The mitoses, however, are no longer present, having disappeared through gradual loss of the estrogen which has not been sufficiently rapid to cause endometrial shedding. If the estrogen levels do drop quickly one may see, such as in the right panel, fragments of stromal breakdown which are rather undistinguished except for interspersed fibrin thrombi. Fibrin thrombi are not a normal component of ovulatory menstrual endometrium. Normal, post-ovulatory menstrual shedding is triggered by apoptotic death of stromal and glandular cells. The appearance of fibrin thrombi within an endometrium with massive stromal breakdown may be suggestive of prior protracted estrogen exposure. This however, is not a sufficiently distinctive feature to allow that particular diagnosis to be made.

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**Superimposed Progesterone**

Sometimes, the changes of unopposed estrogens may be followed by ovulation or modified by the administration of progestational agents. The cystic architecture of benign endometrial hyperplasia may persist, but coexist with stromal and glandular changes of progesterone. In this particular example, we see stromal predecidualization and the development of secretory glands. Yet the architecture is clearly not that of a normal secretory endometrium. Further evidence of the delayed ovulatory process in this patient are scattered fibrin thrombi as seen on the right.

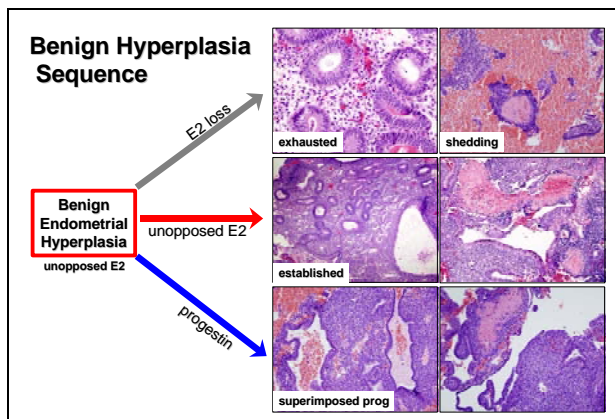
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Histological Features of Benign endometrial hyperplasia					
Feature	Disordered Proliferative	Benign Hyperplasia		Benign Hyperplasia with superimposed progesterin effect	Shedding following Benign Hyperplasia
		active phase	exhausted phase		
mitotic activity	+	+			
scattered cysts	+	+	+	+	
tubal metaplasia	+	+	+	+	
variable gland density		+	+	+	
bulky specimen		+	+	+	
fibrin thrombi		+	+	+	+
microinfarcts with epithelial change		+	+	+	
low or absent mitoses			+	+	+
secretory change				+	+
stromal pre-decidualization				+	+
global breakdown					+

**Microscopic Summary**

This table shows, from left to right, the sequence of individual features which are part of the benign endometrial hyperplasia sequence. Beginning with disordered proliferative endometrium, there are mitotically active tubular glands with scattered cysts and some tubal metaplasia. As the active phase of benign endometrial hyperplasia is entered, the key feature is a variable gland density with several areas having gland area exceeding that of stroma. The specimen becomes more bulky, and develops fibrin thrombi. If the estrogen declines gradually, the endometrial tissue fails to shed and the architectural pattern created by estrogens is now populated by glands without mitoses. This might be described as an exhausted phase. Delayed ovulation, or administration of progestins, can induce epithelial and stromal changes overlying the pre-existing hyperplastic architecture. At the time of massive shedding, many of the distinctive architectural features are lost, and one is left with nondescript fragments of breakdown products and occasional interspersed fibrin thrombi.

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**Benign EM Hyperplasia Sequence**

The notion that the full range of estrogen effects can be described simply as a function of time of estrogen exposure is simplistic. Loss of estrogen leads to mitotically quiescent glands or tissue with massive stromal breakdown, whereas superimposition of progestins alters both glandular density and epithelial and stromal cytology. All of these scenarios contain changes secondary to unopposed estrogen, and we can learn to recognize the distinctive footprint of these hormones even if they are no longer active. The appearance of a biopsy at a single point in time, in a single patient, will thus be uniquely determined by the particular endocrine dynamics for that individual.

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**The Benign Endometrial Hyperplasia Sequence**

**THE END**

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**Conclusion**

This ends our discussion of the benign endometrial hyperplasia sequence. This is George Mutter signing off from [www.endometrium.org](http://www.endometrium.org) in Boston.