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Endometrial Hyperplasia

by

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Signs and Symptoms

It is the woman in the productive age that will come and complain of dysfunctional bleeding, metropathia haemorrhagica and infertility to her gynaecologist. This disease has two peaks in the productive span. The smaller is at the adolescent age and a much higher peak is at the pre-menopausal. The gynaecologist will diagnose endometrial hyperplasia in these cases and a curative or diagnostic curettage is performed. On thistology the curettage would prove to be either

(i) endometrial hyperplasia or

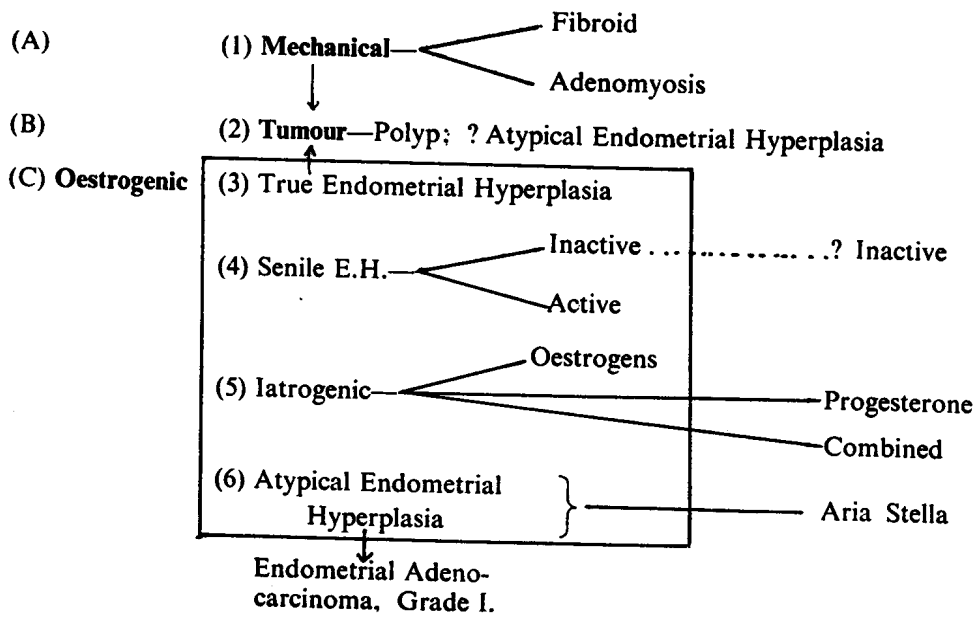
(ii) just an ordinary proliferative phase.

In the case of the latter it may mean that the woman has just bled, and the curettage consists mainly of basal layer or the early regenerative stage of a case of endometrial hyperplasia. Whatever it is, frank secretory changes are not seen in both the hyperplastic and proliferative endometrium.

When the pathologist sees a histological picture of endometrial hyperplasia he would have to run through his mind, with the help of the clinical picture, what the patient may be suffering from. She may be suffering from one of six conditions (see Chart No. 1).

CHART NO. 1

Curettage Giving Picture of Endometrial Hyperplasia May Be Due To



1. Mechanical *(Fibroid & Adenomyosis)*

Endometrial hyperplasia can co-exist with fibroid and endometriosis, and, in fact, figures tend to suggest that the incidence is somewhat higher in these two conditions. On the other hand, I have seen endometrial hyperplasia being locally produced by these two patholo gies. The rest of the endometrium is normal whilst that portion siting on the protruding fibroid or adenomyosis shows evidence of endometrial hyperplasia (Figs. I & II). When multiple fibroids are present in the uterus, endometrial polyps with a hyperplastic picture may be produced by squeezing.

2. Polyp

This is an independent entity of its own, and it is in actual fact a benign adenoma. It starts within the endometrium and does not usually respond to the hormones of the ovary. A few that respond to the hormones, however, are not shed at menstruation, and this benign tumour continues to grow until it attains a polypoid configuration protruding into the uterine cavity and even sometimes out of the cervix. The histology of most of these polyps are identical to a true endometrial hyperplasia, for most of them are not only in the proliferative phase, but also truely hyperplastic. As a matter of fact some of these microscopic polyps are actually part and parcel of a more diffuse endometrial hyperplasia.

3. Endometrial Hyperplasia

The pathologic physiology of true endometrial hyperplasia is due to the fact that a normal biphasic cycle of a woman is disturbed by non-ovulation. We know that a 28-day-cycle woman produces oestrogen from her Graafian follicle in the first 14 days and this hormone stimulates the endometrium into a reparative proliferation after the desquamating menstruation. After the ovulation, progesterone from the corpus luteum prepares the endometrium for implantation of a fertilised ovum, and this second period of 14 days is evinced in the endometrium by a secretory phase, Now, in a woman with endometrial hyperplasia this biphasic cycle is changed into a monophasic one and throughout the period of amenorrhoea only oestrogen is being released from the ovary. The oestrogen may come from one follicle or many follicles but in every case of endometrial hyperplasia, no ovulation and consequently no corpus luteum can be seen in either ovary.

However, this increasing amount of circulating blood oestrogen will reach a state when it will inhibit the F.S.H. of the anterior pituitary. This in turn will put a break upon the production of oestrogen by the ovaries. It is this withdrawal of oestrogen that causes bleeding in the case of endometrial hyperplasia. After the spate of bleeding new Graafian follicles will begin to develop, in respond to the renewed stimulation of F.S.H., and the whole monophasic cycle will start all over again. The point to remember here is that the endometrial picture does not really reflect the severity of the disease or the bleeding; for a non-committal proliferative phase may be accompanied by a most severe bleeding and a very hyperplastic endometrium may be associated with a slightly more than normal bleeding.

Morbid Anatomy of Endometrial Hyperplasia

Grossly, one sees usually a normal-sized uterus but sometimes it may be enlarged. On opening the uterus the endometrium is usually thicker than normal but it may be of normal thickness. In the well established cases we see that the endometrium is rugged, uneven or even polypoid. Although it may simulate carcinoma it may be differentiated from it by the fact that these polypoid, rugged lesions are usually firm and glistening, whereas in a carcinoma it is friable, necrotic and haemorrhagic. In some cases especially after a bout of bleeding we find on closer examination many pits of raw areas.

Histology

Microsocopically, the pathologist must bear in mind that there is a whole range of histological picture which vary between a mere active proliferative phase and a most advanced atypical hyperplasia. He must also bear in mind the fact that only localised areas of endometrium may be involved.

Glandular: The most constant picture is that of a glandular hyperplasia. Here the glands vary very much in sizes and shapes. They may

be dilated, tortuous, straight, small or multilayered (Fig. III) This well known Swiss-Cheese (Fig. IV) appearance would present no difficulty for diagnosis. On closer examination the epithelium has to be tall, broad, with numerous mitoses. Cilia formation (Fig. V) is frequently seen in many glands and in many cases tubal epithelium is closely simulated. In some areas the glands are crowded together, whereas in others they are sparsely populated.

Stromal: In the majority of cases the stroma is also hyperplastic (Fig. III), but this hyperplasia does not hit the eye except in 1-5% of cases. However, the localised crowding of the stroma as well as mitotic figures can be found in every case of endometrial hyperplasia. In the 5% of cases quoted by Schroder, the stromal hyperplasia appears to be a predominant picture with the glandular element taking second place. This is less frequently seen by other authors.

Necrosis & Fibrin: Areas of necrosis due to thrombosed vessels are not infrequently found. Similarly, fibrin masses are quite often seen. These two pictures may simulate a state of post-abortion.

Squamous metaplasia: Squamous metaplasia is quite rare in endometrial hyperplasia. However, when it is seen it does not denote malignancy as some authors would like us to believe.

Lack of secretory change: As expected, it is most unusual to find some evidence of secretory activity. If secretory activity is present one is dealing with either a self-remitting stage of the disease or that of endometrial polyp which is responding to ovarian hormone. Cases have been quoted in literature where early secretory changes in the form of subnuclear vacuolation are seen in conjunction with an early corpus luteum. I have seen subnuclear vacuolation in our cases of endometrial hyperplasia too, but the ovaries are not inspected, and therefore I cannot verify the existence of an early corpus luteum.

Lastly, except for the reaction to the necrotic areas there is an unusual lack of leukocytic infiltration in the endometrium.

The State of the ovary in Endometrial Hyperplasia

It is rare for the pathologist to be able to examine the ovaries at the same time as the endometrium, and the few series reported in the literature show that the ovaries invariably contain multiple Graafian follicles. Some of them are normal, some of them are cystic. It is not unusual to see follicles having 6-12 layers of granulosa. No functional corpus luteum has been reported except in the remitting cases.

The other pathologies are tumours of the ovary, namely:—granulosa cell and theca cell tumours. These tumours form a minority group.

In the cases of postmenopausal women, two other sites of oestrogen production are postulated. One is the adrenal which has been experimentally proven in animals, and the other is the questionable hypertrophied hilar cells of the ovary.

4. Senile Endometrial Hyperplasia

Women must be menopausal for at least a year before they can fall into this category and two histological pictures are seen. One is the active endometrial hyperplasia which looks no different to that seen in the reproductive age. The other is a much more common inactive stage where multiple dilated cysts are seen with a spindly fibrous stroma. The endometrium in this latter category is quite often not thickened. Besides the possible adrenal and hilar cell sources of oestrogen, I have personally noticed some of these cases exhibiting stromal hyperplasia in the ovary. This may be a good line for future investigation.

5. Latrogenic

With the numerous synthetic drugs that are being made in the last decade women taking these drugs present with a bizarre endometrial picture. Therefore, the history of drug taking must always be sought for from the patient before a diagnostic curettage is undertaken. The oral contraceptives and the progesterones would not give any diagnostic difficulties. However, the oestrogens will give a picture no different from that of endometria hyperplasia. Oestrogens are being given to

patients for cancer of the breast, endometriosis and for beauty treatment.

6. Atypical Endometrial Hyperplasia

I will only briefly mention the Aria Stella phenomenon in order to discard it. To an experienced pathologist, the Aria Stella picture means only pregnancy and nothing else. However, uteri have been removed because of this change.

In a small percentage of endometrial hyperplasia we have a histological picture very akin to adenocarcinoma. The glands are crowded in a back-to-back fashion. They show multilayers, luminal infoldings, glandular outpouchings with numerous mitotic figures, and some of these cases are truely adenocarcinoma-in-situ. The other cases may fall into the category of very active endometrial hyperplasia. There is also an atypical change where the cells are large and eosinophiiic or pale in colour. These two benign pictures are seen from time to time in localised areas of endometrial hyperplasia and is not normally seen as a predominant picture. They are interpreted as immature by Novak and malignant by others. However, no matter how experienced is the pathologist, there always will be an isolated case where a definite decision cannot be made and then Halban's phrase of "Not carcinoma, but better out", can then be applied. On this aspect I like to refer to an article published in Cancer Journal Vol. 5, 1952 by Speert in which 16 cases of endometrial carcinoma had previous curettages, ½—22 years before the diagnosis of carcinoma was made. Three were found to be malignant and misdiagnosed in the original curettage, and two revealed normal proliferative endometrium. The remaining eleven all showed atypical endometrial hyperplasia, which, he concluded, must be considered as precancerous especially in the post-menopausal uterus.

Acknowledgements

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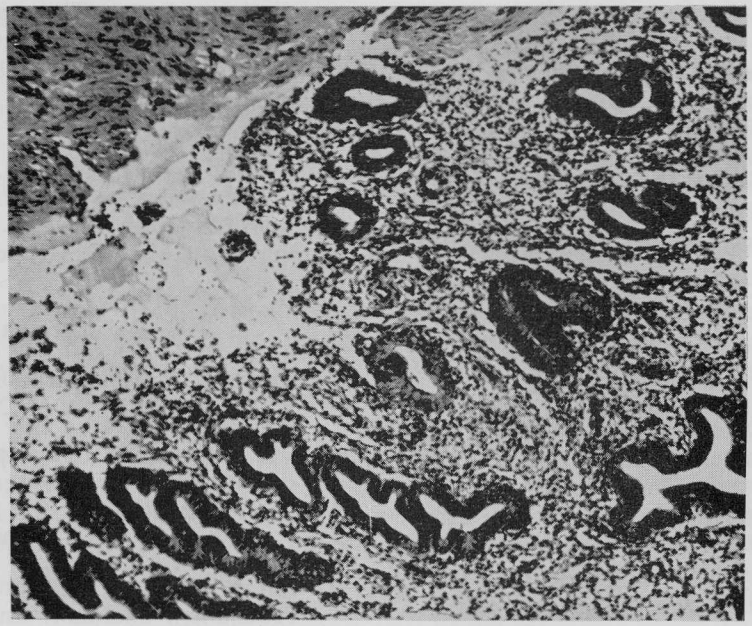

Fig. 1. — x 75

Note fibroid at upper left corner, and rest of field shows early hyperplastic glands.

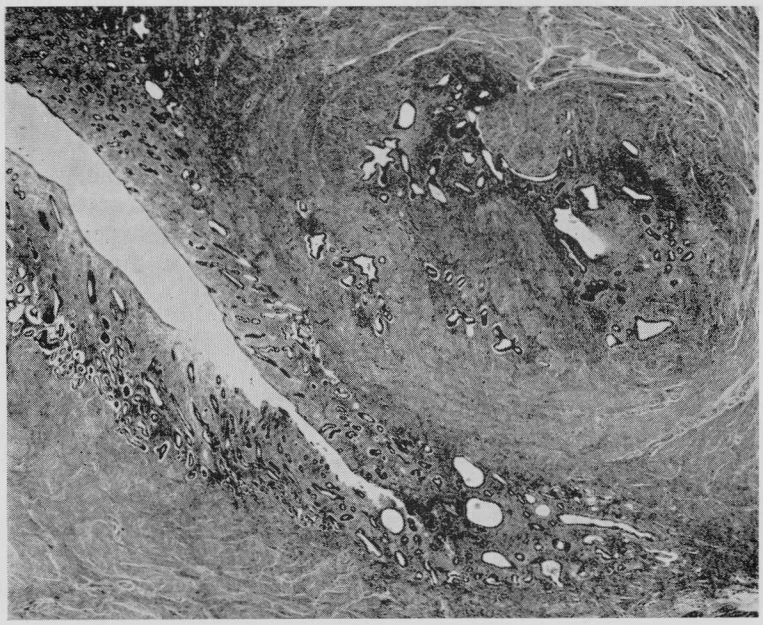

Fig. 2. — x 9

Note adenomyosis pressing on endometrium, producing Swiss-cheese picture of endometrium at bottom of picture.

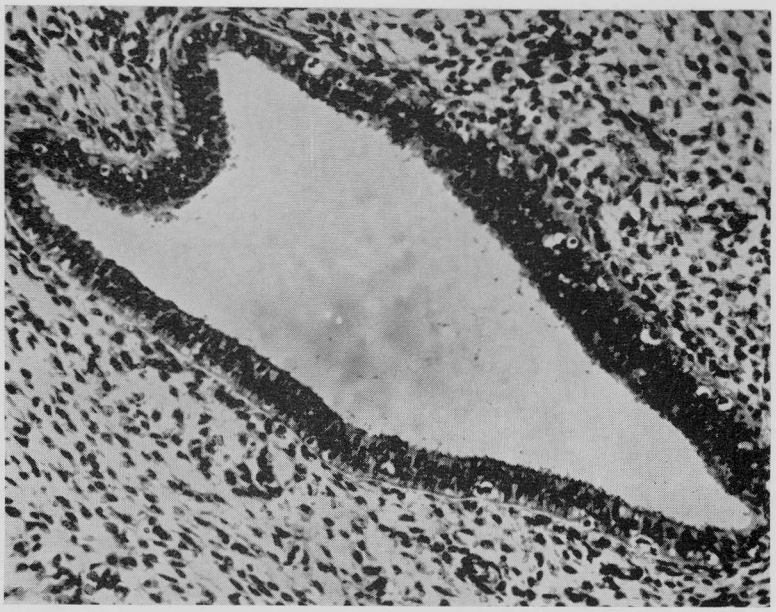

Fig. 3. — x 150

Note multilayering of epithelium and surrounding stromal hyperplasia.

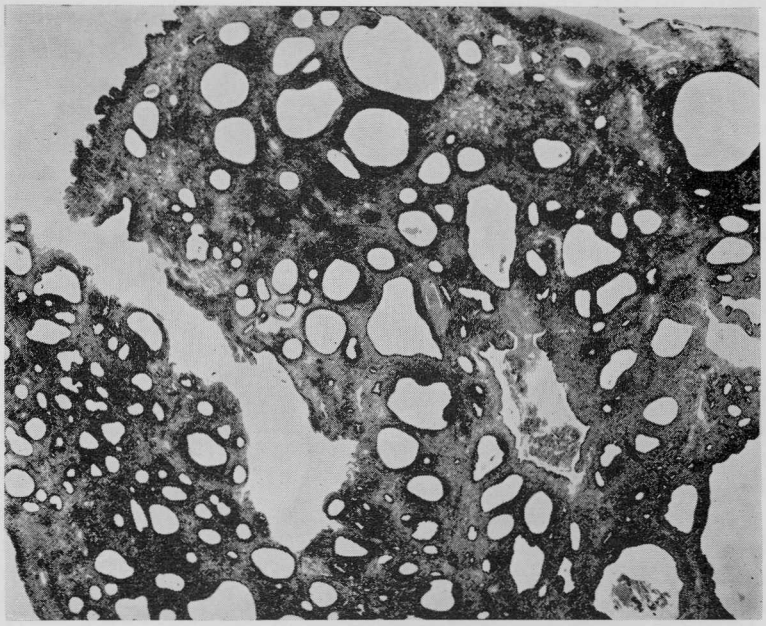

Fig. 4. — x 9

Typical Swiss-cheese appearance.

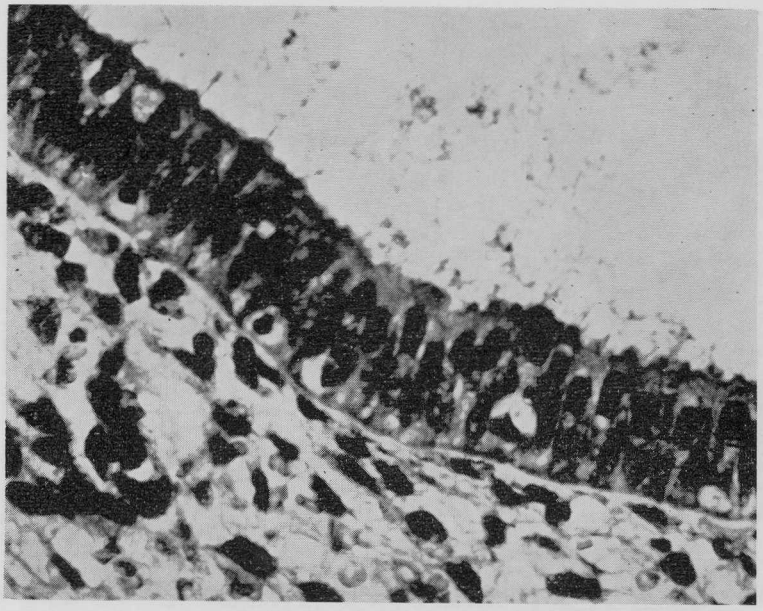

Fig. 5 — x 500

Note tall columnar epithelium with cilia formation.

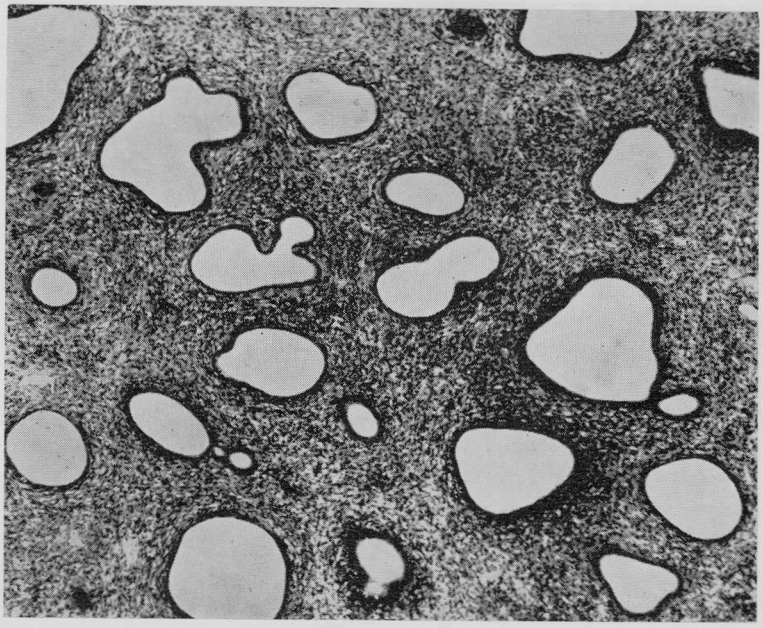

Fig. 6. — x 45

Senile endometrial hyperplasia of the active type.