POST-MENOPAUSAL ENDOMETRIUM

by

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Introduction

Our interest in the appearance of the normal post-menopausal endometrium was stimulated sometime last year when we presented our results of vaginal hysterectomy in the treatment of genital prolapse at a similar meeting. At that time we had studied the incidental pathology of uteri removed at hysterectomy. Many of these patients were well past the menopause, and we were surprised, therefore, to find a varying degree of estrogen activity in the endometrium.

The traditional concept of the senile endometrium is of a mucosa which, having been deprived of its estrogen maintenance, becomes thin, atrophic with shrunken sparse glands, and a scanty fibrotic stroma. It seems to have been assumed that the endometrium like the rest of the genital tract tissues undergoes a simple atrophy.

In post-menopausal gynaecological disorders, particularly the appearance of bleeding, considerable emphasis has been laid on the appearance of the endometrium. The bleeding has been related to the finding of cystic glandular hyperplasia and endometrial polypi. Moreover, the pattern of post-menopausal endometrium, preceding and accompanying carcinoma of the endometrium, has been observed and interpreted in different ways. It must be pointed out, however, that all these suggestions and assumptions have been made without sufficient reference to and study of the endometrial pattern in the normal asymptomatic post-menopausal woman.

The present study deals with three different aspects of the subject:

I. Appearance of the normal post-menopausal endometrium.

II. Source of post-menopausal estrogen.

III. Relation to adenocarcinoma.

Material and Methods

Endometrium obtained from specimens removed at vaginal hysterectomy were studied. Cases where prolapse was the only complaint were included. Cases who had some bleeding or who had received hormone therapy were excluded. The study includes 104 endometria covering a period of 3 years, 1961, 62 and 63.

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Review of Literature

Interest in the post-menopausal endometrium was aroused by 3 studies, that of Breiphol in 1935, Taylor and Millin in 1938 and Novak and Richardson in 1941, all of which reported the unorthodox finding of hyperplasia in a fair proportion of them. Surprisingly high was the incidence of hyperplasia in half of Novak and Richardson's 137 cases.

Despite their great value in awakening interest in the subject, the above reports suffer from two serious short-comings. First and most important is the fact that almost all of the specimens were obtained from women with some gynecological disorder, bleeding being their foremost symptom. Secondly, many of their endometria were classified from curettage specimens. In a significant number no curettage was obtained. Exclusion of these cases, as was done by Novak and Richardson, undoubtedly resulted in a very low incidence of atrophy. On the other hand classification of every endometrium as atrophic solely on the basis of a non-productive curettage, as was done by Breiphol, hardly seems justifiable.

It became apparent then, that to study the normal asymptomatic post-menopausal endometrium, it was necessary to study the entire (hysterectomy) specimen in cases where there was no pelvic pathology, the only possible condition being prolapse.

Gianaroli, Speert and Davies and Williams independently studied the hysterectomy specimens and concluded that functional activity of the ovaries seems to be continued in old age. The largest series so far is that of Parks, Scheerer and Greene from Chicago in 1958. They studied the hysterectomy specimen in 335 selected cases.

The following data were tabulated for each case:

a. thickness of the endometrium,
b. diameter of glands,
c. number of glands per low power field,
d. description of stroma regarding cells, fibres, mitosis and staining reaction,
e. description of glandular epithelium,
f. search for spiral arteries and veins.

On the above basis, the endometria were classified as:

(1) *Atrophic*

a. thin mucosa up to .5 mm.,
b. gland diameter up to .15 mm.,
c. few glands,
d. fibrous stroma,
e. gland epithelium cuboidal to columnar,
f. no spiral arteries,
g. thin-walled veins.

(2) *Inactive Cystic Gland Pattern*

a. endometrium up to 3 mm.,
b. average gland diameter 1.5 mm.,
c. 4-6 glands per low power field,
d. gland epithelium flattened,
e. amorphous material in the glands,
f. no spiral arteries,
g. stroma loose, myxomatous with small spindle cells,
h. thin-walled veins.

(3) *Hyperplasia*

a. thick mucosa up to 6 mm.
b. numerous glands up to 20 per low power field,
c. gland diameter .13 mm. — .6 mm.,
d. columnar epithelium with basophilic cytoplasm,
e. variations in the size of glands,
f. Cellular stroma,
g. mitosis present.

(4) *Proliferative*

a. endometrium averaging 1 mm.,
b. gland diameter approximating .2 mm.,
c. regularity in size of glands,
d. mitotic figures present.

Our study has been based on criteria similar to those of the above authors. Cases of amenorrhoea of one years' duration after the age of 45 years have been included in the study.

1. *Atrophic* 10/104 9.6%

The appearance of an atrophic endometrium is considered normal in a post-menopausal patient. It presumes that menstruation and ovulation came to an abrupt end and that ovulation had continued till the end of menstrual life. The atrophic endometrium is in no way a safeguard against the development of adenocarcinoma, in fact the possibility of missing an early carcinoma in an atrophic endometrium is stressed by the workers from the Mayo Clinic.

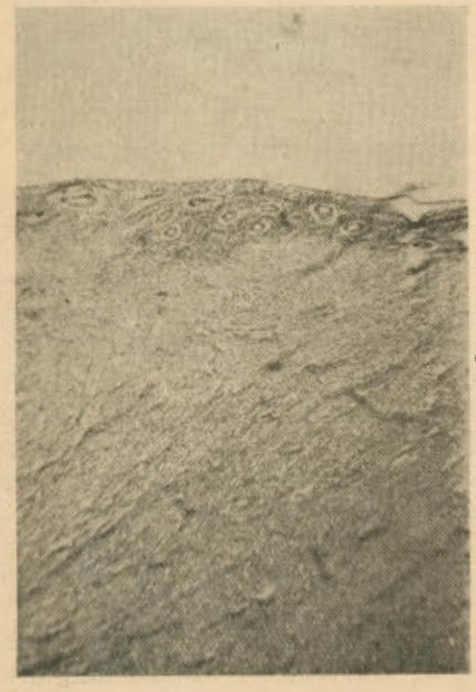

Fig. 1
Atrophic endometrium.

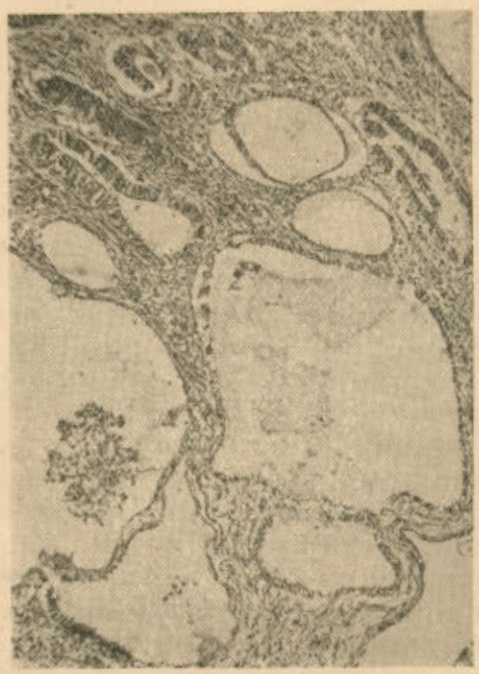

Fig. 2 a
Cystic dilatation of endometrial glands (low power).

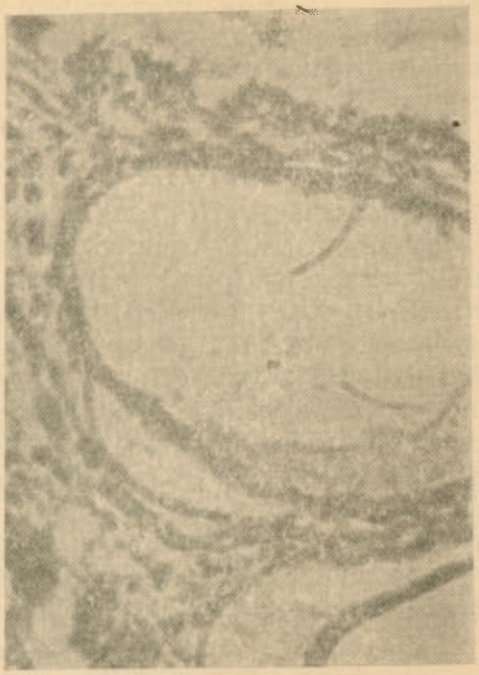

Fig. 2 b
Cystic dilatation of endometrial glands (high power).

2. *Inactive Cystic Gland Patterns* 17/104 15.3%

Cysts of varying sizes were present. The origin and causation of cysts has given rise to much controversy. This 'Swiss-Cheese' type of appearance closely resembles the metropathia haemorrhagica of reproductive life. If the terminal menstrual cycles are anovulatory, this anovulatory hyperplasia stamp will persist throughout the post-menopausal years. It is therefore an evidence of persistence of a previously estrogen-dependent endometrium. The cysts are lined by low cuboidal or short columnar epithelium.

If the epithelium lining the duct is tall, columnar and shows some mitosis, that endometrium is classified as hyperplastic.

Fig. 3
Proliferative endometrium (low power).

3. *Proliferative* 68/104 49.6%

Majority of the cases show a varying degree of estrogen activity as would be found normally in the first half of the menstrual cycle. Some show a moderate and some marked estrogen activity. The source and the amount of circulating estrogen is not important, what is more important is the fact that the endometrium is capable of responding to this stimulation.

If the estrogen stimulation is prolonged and uninterrupted, the proliferative change may advance to that of hyperplasia.

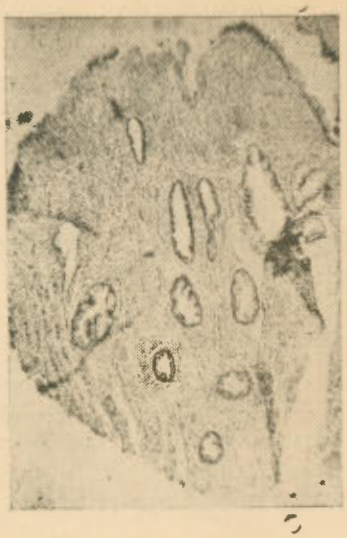

Fig. 4 a
Hyperplasia of endometrium (low power).

Fig. 4 b
Hyperplasia of endometrium (high power).

4. *Hyperplasia* 3/104 2.88%

Frank active hyperplasia is quite rare. It may be either focal in which only a few glands are involved or adenomatous. In adenomatous hyperplasia there are numerous glands practically back to back with very little intervening stroma. The gland epithelium is tall, columnar and shows mitosis.

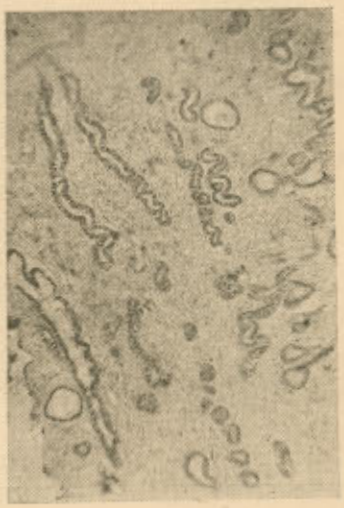

Fig. 5
Secretory endometrium one year after menopause.

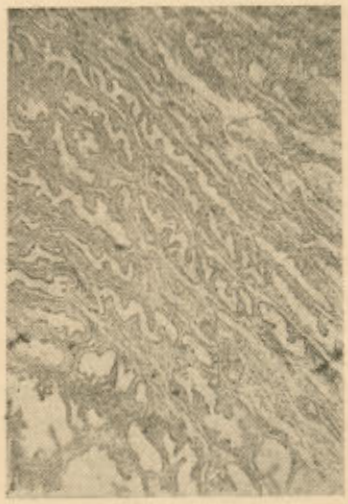

Fig. 6
Secretory endometrium 17 years after menopause.

5. *Secretory* 3/104 2.88%

A progestational pattern in the senile woman is quite rare. Such an

endometrium is ordinarily looked upon as evidence of a preceding ovulation so that it might be looked upon as paradoxical after the cessation of menstruation.

6. *Polyp* 1/104 0.96%

The significance of endometrial polypi is difficult to assess. Very many are innocent although a few may show evidence of malignancy. If the base shows a malignant change, it is considered to be a primary polypoidal carcinoma, while if the tip shows malignancy, it is a secondary malignant change in a previously benign polyp.

50 years. This may in part explain the high incidence of proliferative endometrium, indicating presence of estrogen activity. Ovarian function may continue for 1-2 years after the menopause.

We have not been able to correlate the vaginal cytology with endometrial pattern to double check the presence of estrogen activity.

Table II shows the distribution of cases according to the duration of menopause. This is a more reliable criterion than the age. Most of our patients are not aware of their correct age.

TABLE I

	Atrophic	Inactive cystic glands	Hyper-plasia	Prolife-rative	Secretory	Polyp
Gianaroli, 50 cases, 1950	15%	15%				
Speert, 60 cases, 1949		72%	1.5%			17%
Foix, 100 cases, 1952	6%	80%		10%	3%	
Davies, 40 cases, 1953	40%	30%	25%	5%		
McBride, 1955	60%	20%	5%			
Novak & Richardson, 137 cases, 1941	45.2%	24%	20%	10%		
Parks, 337 cases, 1958	49.6%	48.9%	.9%	.3%		
Present series, 104 cases, 1964	9.6%	15.3%	2.8%	49.6%	2.8%	.96%

Table I gives the incidence of various types of gland patterns as compared to other authors.

From this table it is obvious that incidences vary widely in each series. Our results can be compared to those of Parks. We have a significantly high incidence of proliferative changes. However, it must be pointed out that proliferative and inactive cystic gland pattern may overlap in quite a few cases.

Our patients belong to a younger age group, 34 being under the age of

TABLE II

Duration of menopause	No. of cases
Under 5 years	34
6-10 years	21
11-10 years	24
16-20 years	16
Over 20 years	9
Total	104

Table III shows the incidence of the various types of endometrium according to the duration of menopause.

TABLE III

Years after menopause	Total No. of cases		(1)		(2)		(3)		(4)		(5)		(6)	
	McBride	P. S.	McBride	P. S.	McBride	P. S.	McBride	P. S.	McBride	P. S.	McBride	P. S.	McBride	P. S.
	206	104												
Under 5 years		34	31.8	5.8	23.1	11.6	27.5	—	11.2	76.8	5.5	2.9	—	—
6-10 years		21	37.2	19.2	53.5	24.0	—	—	2.3	57.0	6.9	—	—	—
11-15 years		24	27.6	12.5	58.6	8.33	—	4.17	—	75.0	13.8	—	—	—
16-20 years		16	24.1	18.8	65.5	25.0	3.5	12.5	—	37.4	6.9	—	—	6.25
Over 20 years		9	38.1	—	6.19	11.1	—	—	—	88.9	—	—	—	—

Note: P.S.: Present series.

All comparative figures are in percentage.

1. Atrophy. 2. Inactive cystic gland pattern. 3. Hyperplasia. 4. Proliferative. 5. Fibroadenomatous polyp. 6. Secretory.

Our figures are compared with those of McBride published in 1954. It is significant that 88.9% of women with a menopause of more than 20 years' duration showed a proliferative endometrium.

It is also interesting to find that in the 2 cases of secretory endometrium, one was 1 year after the menopause and the other 17 years after the menopause.

II. Source of Post-menopausal Estrogen

It may be either exogenous or endogenous. Endogenous sources may be the ovary, the pituitary or the adrenal.

Very few references are available in the literature on this subject. Presence of estrogen activity has been well established by now, but the source of that estrogen is still a debatable question.

(a) *Ovary*

In 1954, Shelton referring to the use of estrogen in the post-menopausal woman, described certain types of women who may cease to menstruate but who continue to elaborate a submenstrual level of estrogen for an additional 10-15 years.

Struthers et al., in 1956, reported in the B.M.J. a series of 353 post-menopausal women in whom 53% showed good estrogen activity. They conclude:

a. Estrogen production is not affected by the manner in which the menopause is achieved.
b. Neither the ovary nor the adrenals are found to be a significant source of estrogen after the menopause. Castrated and adrenalectomised females have shown equal estrogen activity.
c. Estrogen does not appear to play an important part in cancer.

Novak and Yui are convinced that the functional activity of the ovary persists for a time especially so far as the production of estrogen is concerned. This is comparable to the prepubertal development of follicles and production of estrin followed later by anovulatory or ovulatory cycles which so often characterise the inauguration of menstrual function at puberty.

In recent years ovarian cortical stromal hyperplasia has been mentioned as an important source of estrogen. Hyperplasia of the connective tissue of the ovarian cortex was first described in 1941 by Smith, who noted that this anatomic change in the ovary was often associated with adenocarcinoma of the endometrium. Donald Mckay reviewed the present status of this hypothesis in Progress in Gynaecology Vol. III.

In the present series an attempt was made to study the ovaries, to evaluate the presence of ovarian cortical stromal hyperplasia. The number of ovaries available for study were very few and no conclusions could be reached.

The cortical stroma is composed of a special connective tissue cell characterised by its spindle shape, elongated nucleus and a relative lack of collagen fibres. Occasionally these cells undergo an alteration referred to as thecomatosis. This cortical stromal cell is capable of secreting estrogenic hormone.

(b) *Pituitary*

Novak has suggested that the pituitary may assume estrogenic function after menopause. This theory is supported by the report of Frank and Goldberger on the urinary excretion of the estrogenic factor in 12 surgical castrates, Hoffbauer's stimulation of the basal endometrium in castrates with anterior pituitary extracts suggests that post-menopausal estrogen may arise from anterior lobe stimulation.

(c) *Adrenal*

Adrenal steroids have an estrogenic effect. On experimental data available, the adrenal glands are the most likely source of oestrogen.

III. Relationship of Endometrial Hyperplasia to Adenocarcinoma of the Endometrium

Serious interest in the subject was first expressed in 1932 when Howard Taylor Jr. reported his observations on the relationship of these two conditions. For the last twenty years many authorities have presented their evidence for and against the possible relationship.

Taylor, in 1932, concluded that the histological differentiation of hyperplasia from certain types of carcinoma may be difficult and that the possibility in the errors of diagnosis may lead to disastrous results. He further concluded that when hyperplasia was marked the case should be regarded with some suspicion.

In 1936, Novak and Yui indicated that there was some sort of relation between the two conditions, particularly in the post-menopausal woman. They have reported the coexistence of adenocarcinoma and hyperplasia in one and the same case. Moreover in one and the same section they have noted all grades of transition, from frankly benign to borderline and to obviously malignant histological pictures.

In 1947, Gusberg called attention to a pattern of adenomatous hyperplasia of the endomentrium which bore a constant relation to estrogen stimulation. He also believed that he could observe a graded progression from adenomatous hyperplasia to malignancy.

In 1949 Hertig, Sommers and Bengloff made an extensive study of the genesis of endometrial carcinoma. Starting with 500 cases of carcinoma, they studied 67 cases in which curettages done 1-23 years previously, were available. A great majority of these revealed an antecedent hyperplasia. They subdivided the hyperplasias into focal and adenomatous. They concluded that adenomatous hyperplasia may be a precursor of carcinoma. They described carci--noma-in-situ of the endometrium and reported six such cases, in which invasive carcinoma developed from 1-11 years later.

In 1952, Speert published an excellent paper on "The premalignant phase of endometrial cancer". Among 13 cases, in which curettage obtained previously was available, only two were normal while 11 revealed hyperplastic gland patterns. Speert regarded these hyperplasias as distinct from ordinary functional hyperplasia as did Novak, and concluded that this type of hyperplasia

should be regarded with grave suspicion.

Te Linde, Jones and Galvin, in 1953, attempted to evaluate the present status. They divided their cases into 3 groups.

I. In 13 cases curettage report was "marked adenomatous hyperplasia, malignancy doubtful". Ultimately a hysterectomy was performed by the surgeons so as to be on the safe side; 11/13 showed a definite carcinoma in the hysterectomy specimen.

II. In 14 cases report was "some hyperplasia, malignancy doubtful." No definite treatment was undertaken. A recurrence of symptoms required a second curettage, which in all cases showed definite malignancy.

III. Retrospective study of 8 cases of carcinoma, in which previous curettage was available for study, revealed various types of endometrium.
3 cystic hyperplasia,
2 secretory,
2 pre-menstrual,
1 post-menstrual.

The latest report on the subject is in 1963 from the Mayo clinic. Butler, Dockerty and Randall studied 2% of 3000 cases of carcinoma in whom slides of a previous curettage were available. They concluded that:

a. Carcinoma can originate in a proliferative, secretory, atrophic or hyperplastic endometrium, or even in a polyp.

b. The significance of gland hyperplasia in pre- and post-menopausal endometrium is different, the time interval between the development of hyperplasia and adenocarcinoma being shorter in the post-menopausal than in the pre-menopausal woman.

c. Of significant importance is the fact that carcinoma is more likely to be missed in the post-menopausal atrophic endometrium.

The impact of the above discussion on the clinical management of these cases is of prime importance. Te Linde and Novak, both from the same Institute, seem to hold opposite views. While Novak is convinced of the dangers of post-menopausal endometrium, Te Linde is more conservative. He says, "if we are to change our concept of hyperplasia from a purely benign lesion to a precancerous one, the next logical step would be to change our present conservative treatment in a radical direction." This he feels would be a mistake, and it is with the thought of preventing unnecessary radical surgery or radiation that he has brought up some objections.

We have no view to offer on the subject, not having come across any cases of endometrial cancer. Our series consists essentially of asymptomatic patients. In the 3 cases of hyperplasia included in this series the changes were not marked. The type of patient who is susceptible to adenocarcinoma is essentially one with obesity, hypertension, diabetes and relative infertility. Our patients fall into an opposite group. They were all parous women who were good operative risks.

However, in view of the evidence presented, it would seem justifiable

to perform a total hysterectomy with bilateral salpingo—oophorectomy in a post-menopausal woman with vaginal bleeding, in whom the curettage shows hyperplasia. Further treatment would depend upon the histopathology of the hysterectomy specimen.

Discussion

Though the traditional concept of the post-menopousal endometrium was one in which it had become thin and atrophic, with a fibrous stroma and small inactive glands, it has been proved beyond doubt by various authors that this is not so, and that other types of endometria are seen long after the menopause. The incidence of *atrophic* endometrium varies, but it is usually present in 3/4th of all menopausal patients. In this study, however, the incidence was only 9.6%. This low incidence can be explained by the fact that these cases were all operated specimens. If, as McBride suggests, all patients where curettage produced no endometrium are added, this incidence will be higher.

Inactive cystic gland pattern occurred in 17 patients (15.3%). A very plausible explanation of the presence of these cysts is offered by other authors, especially Speert. He describes them as "retention cysts" following occlusion of their ducts. The stroma around the necks of the glands and ducts undergoes fibrosis and results in cicatricial blockage of their ducts. He considers it a very harmless passive distension of the glands. The stroma is inactive. His views are not supported by Novak.

There is a discrepancy between the incidence of *proliferative* endometrium (49.6%) as compared to other authors where the incidence varies from 5-10%. It is difficult to find an explanation for this, though it is possible that the addition of cases with non-productive endometrium would increase the incidence of atrophy and reduce the incidence of proliferation. In the present series the patients are also of a younger age group, 34 being under the age of 50 years. A third possible factor may be the vascular disturbance caused by the prolapse.

Hyperplasia was present in 3 patients (2.88%) in the present series, all cases occurring between 11-20 years after the menopause. In McBride's series, the majority of cases of active hyperplasia occurred within a few years after the stoppage of menstruation.

Secretory endometrium was present in 3 patients (2.88%). This is a rare picture. Novak has found it on 2-3 occasions. Occasional spontaneous ovulation 1 year after the cessation of menstruation has been described. This explains one of the present cases. The amenorrhoea in this case is considered to be of hypothalamic origin. Another explanation given by Novak is that certain cases of hyperplasia may simulate a secretory endometrium. Differential diagnosis may be difficult even for a trained pathologist. A third explanation is that given by McKay of the Harvard School. He showed that early adenocarcinoma has the histochemical appearances of a progestational endometrium. The finding supports the possibility of an influence of a progesterone-like hor-

mone in the genesis of human endometrial carcinoma.

The incidence of endometrial *polyp* in this series was 0.96%. Polypi may be found in the uteri of asymptomatic post-menopausal women, even in the presence of an atrophic endometrium. Various authors have explained the presence of polypi on a mechanical basis, an inflammatory change or a benign tumour. Its presence with endometrial hyperplasia suggests a common hormonal factor in such patients and points towards abnormal oestrogen activity. Novak and Richardson suggest that polypi represent previous hyperplasia at the time of the menopause, in which retrogression has occurred. If this is true, a number of these women should have had an abnormal menopause, with excessive bleeding. This has not been proved by other workers. Unfortunately the previous menstrual histories in the 3 patients with hyperplasia and the 1 patient with a polyp had not been noted and so no co-relation made. Chronic irritation leads to polyp formation. Chronic irritation is also a proved carcinogenic factor. In the cancer-prone post-menopausal woman the chances of malignancy developing are particularly high.

Summary

1. A study was made of the endometrial pattern in 104 post - menopausal women whose uteri were removed during a vaginal hysterectomy for prolapse. All patients who had bleeding or hormone therapy were excluded from the study.
2. The incidence of atrophic endometrium was 9.6% inactive cystic gland pattern 15.3%, hyperplasia 2.88%, proliferative 49.6%, secretory 2.88% and polypi 0.96%.
3. Literature on the subject has been reviewed and an explanation has been attempted on the presence of the various types of endometrium.
4. The source of post-menopausal oestrogen is discussed and also the relationship of endometrial hyperplasia to adenocarcinoma of the endometrium.

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