THE MENOPAUSE

- by -

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C O N T E N T S.

THE MENOPAUSE.

THE OBJECT OF THE INVESTIGATION.

The aim of this investigation was to collect and correlate facts on the changes which occur in women who have passed the menopause, whether it be normal or induced artificially. Particular attention has been paid to the main symptoms of the menopause, viz: flushing of the face, and to the changes in the genital tract.

At the outset it is necessary to state what is known of the anatomy and physiology of the genital tract in normal women at the reproductive period, in order to compare this with the changes after cessation of menstruation.

It may be assumed that the normal variations in the genitalia of a woman at the reproductive period are sufficiently well known to be passed over. The vagina, however, requires special mention, since there exists great differences in opinion as to the normal histological appearances and physiological changes which may be observed in the mucosa.

Chapter I.

THE ANATOMY OF THE VAGINAL MUCOSA AT THE REPRODUCTIVE AGE.

Bloom (34) describes three layers in the vagina, a lining mucosal layer, a middle (muscular) and, deepest, a fibrous or adventitial coat. Consideration here will be confined to the lining mucosa. This consists of a deep layer of connective tissue (Lamina Proprium) with a variable number of small blood vessels and lymphatics; numerous lymphocytes are to be seen in the stroma. The superficial or lining layer of the mucosa consists of stratified squamous epithelium. The histological appearances vary with the age of the patient, and whether or not she is pregnant. A chart from Davis and Pearl (7) shows the accepted appearances.

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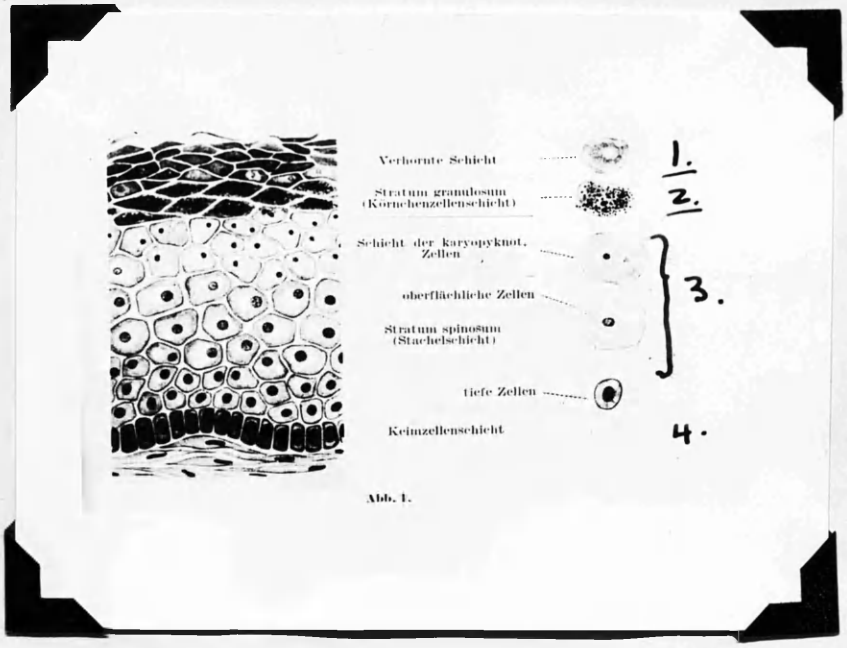
	Newborn	Month old Child	Puberty	Sex-Mature	Post-Menopause
Estrogenic hormone	+	−	appears	+	−
Epithelium					
Glycogen	+	−	− to +	+	−
Acidity	acid pH 4-5	alkaline pH 7	alkaline → acid	acid pH 4-5	neutral or alkaline pH 6-7
Flora	sterile? Doderlein's bac. (secretion abundant)	sparse, coccal and varied flora (secretion scant)	sparse, coccal → rich bacillary	Doderlein's bacilli (secretion abundant)	varied flora (secretion scant)

Murray (24) and others (52), (32), (12) accept Dierks' view that the stratified squamous epithelium of the human is a three-layered structure, viz: a superficial layer and intermediate "keratinised" layer (constituting the "functionalis"), a stratum spinosum and deep basal layer. The keratinised layer is so called because of its staining properties, the "functionalis" is so called because it is shed at the menses. The following is a diagram from Murray (24).



(1). Superficial keratinised layer; (2). Interstitial keratinised layer; (3). Stratum spinosum; (4). Stratum germinativum.

Zondek (8), Stemshorn (48) and Gisbertz (46) disagree with this view. Zondek for instance found a completely different histological picture in biopsies

taken from various sites in the vagina. Stemshorn found that the epithelium has no such definite layers, but that roughly three types of cells exist; the most superficial cells are large and have a small or absent nuclei, the middle layers have a smaller amount of cytoplasm but show larger nuclei, while the basal layer consists of small well nucleated cells on a basement membrane.

The conclusion drawn from the literature is that great difference of opinion exists on the precise histology of the vaginal mucosa of the normal woman at the reproductive period, so that difficulty arises in comparing the changes in the menopausal mucosa with that of the reproductive years.

Our own investigation of the vaginal epithelium in sexually mature women is limited to 13 cases. In all but one case the type of epithelium seen corresponded to that described by Stemshorn, having only three differentiated layers. The exception had only two layers, a stratum germinativum and a stratum spinosum, the superficial layer being absent. In order to obviate the difference in appearance between sections stained with Best's glycogen stain and haematoxylin-oesin, both methods were used. No layer resembling an "Interstitial keratinised layer" was found, nor was such a layer seen in the post-menopausal series.

It must be mentioned, however, that a specimen found in our Midwifery Department's collection (Fig. 3) showed appearances akin to that described by Murray and Dierks.

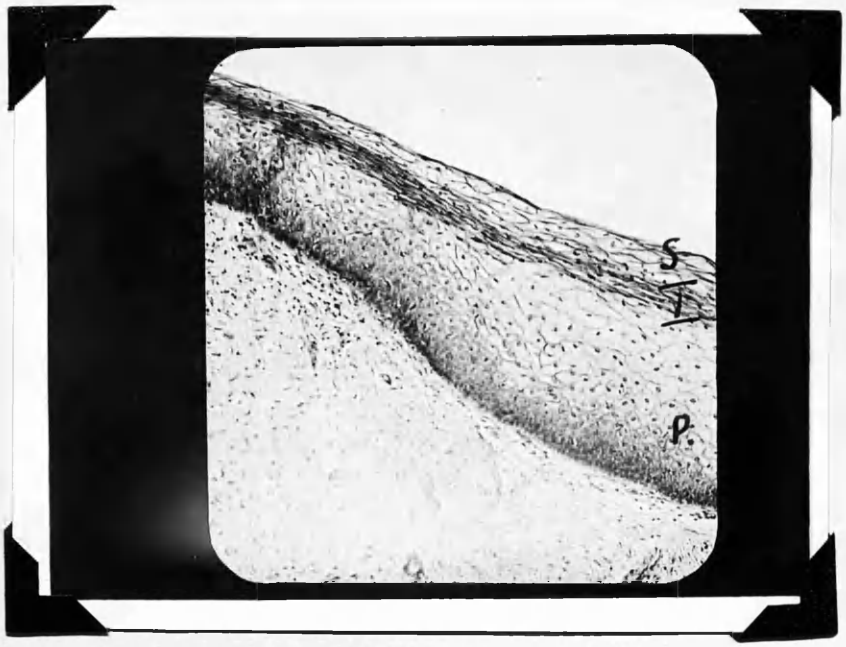


Fig. 3. H. & E. staining. X 94.

Interstitial keratinised layer (I) shown between superficial layer (S) and deeper stratum spinosum cells (P).

In conclusion, our views tend to support Stemshorn et alii, but great disagreement exists in the literature regarding the precise histology of the vaginal mucosa in the sexually adult woman at the reproductive stage.

PHYSIOLOGY OF THE VAGINA (In normal women of reproductive Age.)

It is known that the genital tract arises mainly from the mesodermic masses known as the Ducts of Müller (1). The fact that the uterus and fallopian tubes (32), (37)

are under ovarian control, led one to expect that the vagina was similarly controlled. But to what extent the ovaries control the vaginal mucosa is still in doubt.

Long and Evans (2) in 1921, showed that in the vagina of the rat there occurred a regular building up of the lining epithelium followed by desquamation. The ovaries controlled this activity, and when the animal was in heat or oestrus, the mucosa was at its maximum thickness. A similar ovarian-controlled cycle affecting the vaginal mucosa of the cow (5), pig (6) and ape (8A) has been demonstrated.

Many authors (18), (22), (24), (32), (52) support the theory that, in the normal sexually adult woman, the vaginal epithelium is built up before each menstrual period, to be shed, at least in part, at the onset of menstruation. An equal number of authors (8), (12), (46), (48), (49) can be found to refute this theory, so that the question of a monthly vaginal cycle is at present sub judice. We have no views on the question based on experience, since it is extremely difficult to obtain vaginal biopsies at even weekly intervals from the same patient. The problem will be difficult to solve, and we are of the opinion that the examination of smears of the human vagina may be grossly inaccurate in their forecast of the epithelium, so that we doubt the value of this method of solving the problem.

The following diagram gives, in brief, our present knowledge of the link between the anterior pituitary hormones, oestrin and the vaginal mucosa:-

ANTERIOR PITUITARY HORMONES
↓
OVARIES
↓
OESTRIN
↓
VAGINAL MUCOSA inc. Thickness
↓
GLYCOGEN DEPOSIT increased
↓
LACTIC ACID (pH 4.2)
↓
DODERLEIN B.

Bourne (65) believes that the lactic acid of the vagina is mainly produced by the action of B. Doderlein in the mucosal glycogen. Against this is the fact that the vagina at birth has abundant lactic acid (13), yet no Doderlein B.; moreover, attempts at formation of lactic acid with B. Doderlein and Glycogen in vitro, have failed. It seems most likely that B. Doderlein is an infection originally, and that it grows well in the suitable medium provided by the vagina.

Although both the normal histology and the question of cyclical changes of the mucosa have not yet been settled, there exist groups which show widely varying

ovarian effects on the mucosa. For instance, in pregnancy (7) the ovarian hormones are maintained at a high level with a resulting florid, thick, vaginal epithelium, loaded with glycogen, and, usually, a pure flora of B. Doderlein. Figures 4 and 5 show epithelium and smears from a normal pregnant woman.

Fig. 4. Vaginal biopsy. Best's stain, mgfn. X 60. (Glycogen shows black).

Mrs. M. Full term: Florid epithelium loaded with glycogen.

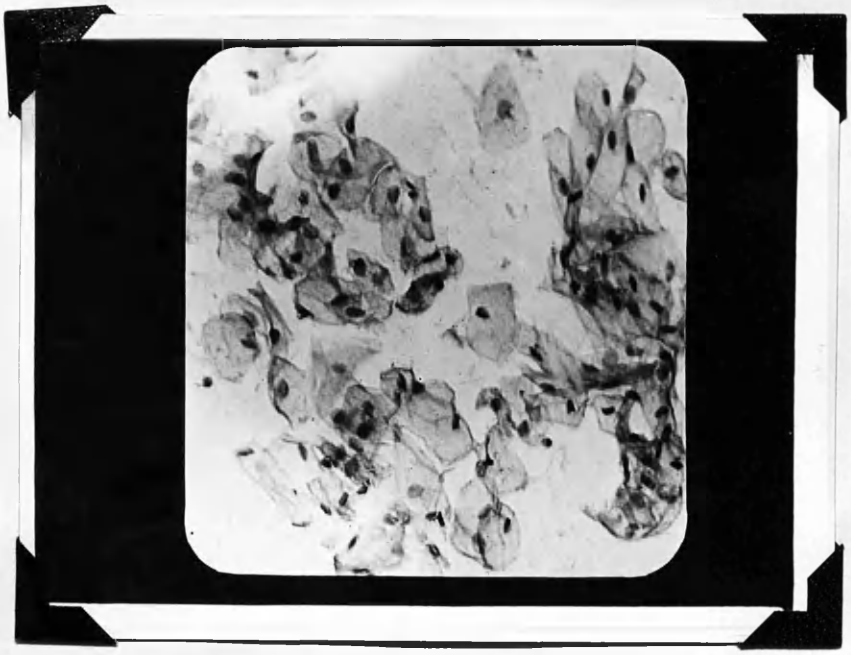


Fig. 5. Vaginal Smear of above case stained by Papinicolau's method. X 224.

Flat squames mostly with nuclei (Grade III).

Again, in the new born (Figs. 6 & 7), the influence of maternal oestrin is seen in the thickness of the epithelium, which, moreover, has much glycogen throughout its layers.

Fig. 6. Vaginal Biopsy: Best's Stain X 60.

Thick Epithelium from a still-born full-time foetus, showing much glycogen.

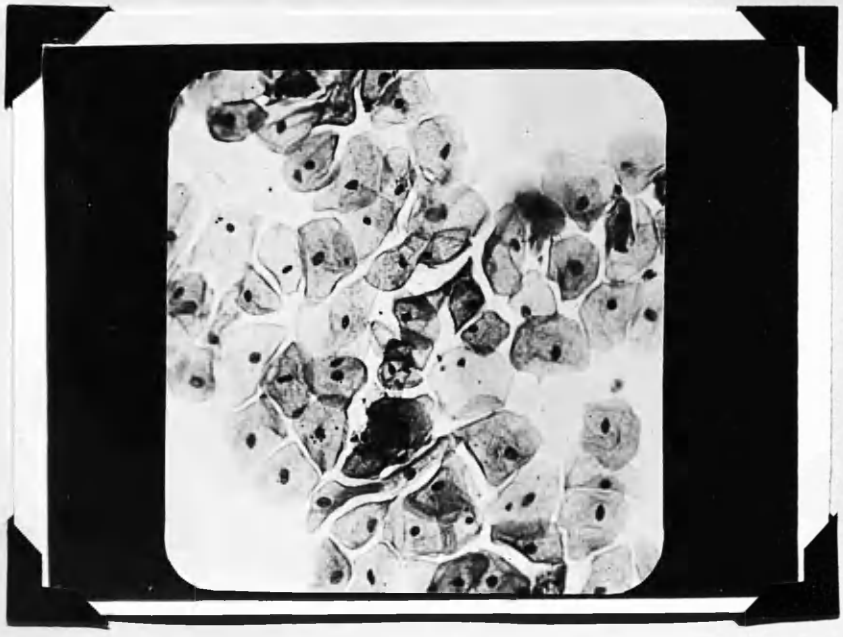


Fig. 7. Smear of above epithelium. X 224.

Grade III. Note the lack of organisms.

The gross deficiency of ovarian activity is evident in the type of smear picture and from the vaginal histology in some cases of amenorrhoea.

Fig. 8. Vaginal Biopsy: Best's Stain X 60.

Miss S: Primary amenorrhoea with infantile uterus.

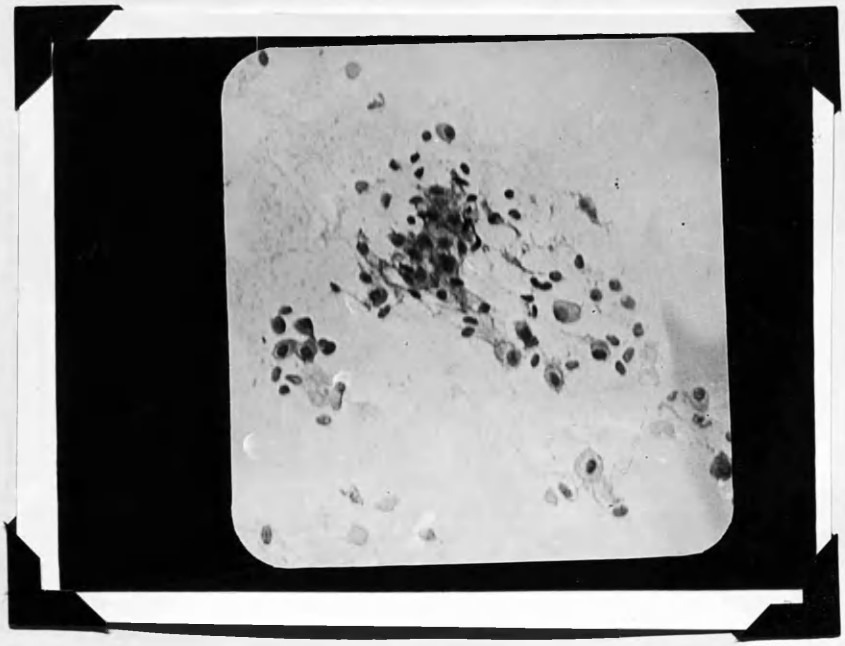


Fig. 9. Miss C. Vaginal smear: Papinicolau's Stain. X 224.
Primary amenorrhoea: uterus infantile. Cells of small type (Grade I). No pus or flat squames.

To summarise, the different effects brought about by oestrin acting on the vaginal mucosa are easily demonstrated in sharply contrasting groups, such as pregnancy and primary amenorrhoea. In the sexually mature woman however, neither the problem of the precise normal histology, nor the presence or absence of cyclical changes of the mucosa, have been worked out conclusively.

Chapter 2.

THE PHYSIOLOGY OF THE MENOPAUSE.

A. AMENORRHOEA.

After cessation of the periods the menopause commences, and this meaning of the word is adhered to; the wider term, climacteric, is taken to mean the period when there may be flushing and irregular menstruation, signifying that the menopause is about to commence.

It is unnecessary to go into details of the normal, sexually adult female's hormone picture as it is understood to-day. Suffice it to say that there exists a "circle" of interacting hormones; the anterior pituitary gland activates the ovary, which forms ova. The graafian follicle which contains the ovum produces oestrin and, later, by changing its state to a corpus luteum, produces progesterone. The effect of these last two hormones on the uterus is well known, and the resulting thick endometrium is shed at the time of menstruation. At the menopause menstruation ceases. Is it the pituitary gland, the ovaries or the uterus, cervix & vagina (the so-called end organs) which fail to maintain their former activity?

The end organs can function after the menopause. Davis & Koff (60) have produced true menstruation

(i.e. with the formation of pseudo-decidua) in a castrated woman by administering oestrin and corpus luteum hormone. The effect of oestrin on the cervix and vagina of the menopausal woman is to produce the appearance of a sexually mature woman. So that the end organs will apparently act if stimulated by the appropriate hormones.

The anterior lobe of the pituitary is active, and Fluhman and others have shown that larger amounts are excreted in the urine of menopausal women than in the normal woman. The excretion of urinary oestrin however, is usually lower in the menopause, and may be absent (Shute (71) et al.). It is suggested by this evidence that the amenorrhoea is due to the failure of the ovaries to function normally. The ovaries do not cease completely to function (for Shute has actually shown that in 12 cases a definite surge and fall of urinary oestrin can be demonstrated over periods of months), but they no longer accept the full stimulus of the anterior pituitary hormone to form ova, or even graafian follicles. Albright (72) therefore defines the menopause as a "Physiological ovarian amenorrhoea" in contra-distinction to other types of hypogonadism where, for instance, the anterior lobe of the pituitary may be at fault, and this would appear to be the accepted view of the amenorrhoea of the menopause.

B. SYMPTOMS OF THE MENOPAUSE.

The age of onset of the menopause averaged in our series, 46 years, but it varies from the "30's" to the "50's" from case to case. There may be no symptoms. (In our cases several of this type had late pregnancies, after which amenorrhoea persisted). Usually, however, the menopause is heralded by the onset of symptoms, and these may persist for years after. Three groups of disturbances are described by Whitehouse (68).

(1). Vasomotor.
(2). Metabolic.
(3). Psychical.

(1). The most common example is a sensation of heat passing over the face and, even, the whole body; the skin may be obviously flushed and, in severe cases, beads of sweat may appear before the flushing passes off. Flushing was found to be the most typical and easily assessed symptom of the menopause. Headaches, neuralgia, throat sensations, etc. which may be related to the vasomotor upset of the menopause, were seldom found or noticed for the first time at the menarche or menopause, although the latter may have aggravated the symptoms. In consequence these symptoms have been noted, but were difficult to assess properly.

(2). Adiposity (again difficult to assess unless weight cards are available), is an example of metabolic upset at

the menopause. It is common indeed, but frequently the increase in weight commences long before the menopause, and may not be related to the latter in every case. (3). Irritability, nervousness, etc. are examples of psychical disturbances at the menopause. Obviously all outside factors must be allowed for before the menopause, per se, is blamed; e.g. the patient's attitude to her husband or children may be unsatisfactory and may explain a good deal of her "nervousness". We gave up trying to assess this symptom, for the subjective evidence of the patient alone was of little value.

The relation between the symptom of flushing and the hormones in the menopausal woman has not been worked out conclusively, there being much contradictory evidence. Albright suggests that flushing may be caused by -

(a) lack of ovarian follicular hormone,
or (b) excess of A.P.H. (anterior pituitary hormone),
or (c) an unknown factor.

(a). The lack of oestrin due to "ovarian failure" or removal of both ovaries is an attractive theory, but menopausal (51) and castrated women (63) both produce a substance resembling oestrin in the urine. The amount produced is less than normal, but may be quite consider able. The substance produced in castrated women,

obviously not from the ovaries, must come from another source. That the ovarian deficiency, although not a complete deprivation,may be related to flushing, is suggested by the fact that administration of very small doses of oestrin will usually relieve flushing. Fluhman (63) however, tested 82 patients with flushing of varying intensity; of these 23 were castrated, 4 had radium, 30 had at least 4 months of amenorrhoea and 25 were at the climacteric but had occasional periods. Although 65 out of 76 had definitely oestrin in the urine, no correlation was found to exist between the presence of oestrin and the severity of flushing, e.g. of 30 cases with mild flushing, 5 had no oestrin excretion in the urine, while 6 out of 8 cases with severe flushing, had oestrin in the urine. Fluhman therefore concludes that the presence or absence of oestrin in the urine of menopausal women, or women approaching the menopause, bears no relation to the symptom of flushing.

(b). Excess of A.P.H.[x] in the circulation has been suggested as the cause of flushing. Fluhman showed that the more serious the degree of flushing the higher was the percentage of cases showing positive urine tests for A.P.H. (This test is, of course, negative in the non-pregnant sexual adult.)

The relation between oestrin and A.P.H. excretion has been worked out with exactly opposite findings by

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x Anterior Pituitary Hormone.

Schafer (62) and Heller (64). The first named believes that urinary excretion of A.P.H. is diminished by oestrin therapy, but Heller refutes this. It appears that this interesting point is at present undecided.

(c). The "unknown factor" causing flushing is hypothetical. Male hormone when given in large doses to a normal woman of reproductive age will produce flushing (62), the latter being easily controlled with oestrin therapy. (Male hormone, moreover, given by injection to two normal males in large doses, produced flushing). Paradoxically, the same author (62) showed that menopausal flushing in castrate or menopausal women can be controlled by testosterone if given in large doses. Schäfer believes that flushing is related to excessive secretion of anterior pituitary hormone and attempts to explain the effects thus: "In a castrated or menopausal woman A.P.H. is in excess in the circulation, the male hormone will diminish this and so control flushing. In a normal (sexually adult woman) however, the Ovaries are acted upon with male hormone, resulting in a diminished output of oestrin and a rise in the amount of A.P.H. in the circulation and, subsequently, the onset of flushing."

The cause of flushing has not been explained on the basis of our present knowledge of hormone secretion. The above discussion however, shows some of the conflicting theories which exist and the difficulty of coming to a conclusion on the matter.

C. CHANGES IN THE GENITAL TRACT IN THE MENOPAUSE.

It will be shown later that marked changes of the anatomy of the genital tract become more common in the older menopausal women, although the individual degree of change may vary strikingly from case to case. For example, a menopausal woman of 48 with a tensile roomy upper vagina may manage to wear a ring pessary for a slight prolapse in comfort. At 68 however, two difficulties arise: (a) she may not manage even a small pessary into the fornices, and (b) if she does manage, the mucosa is easily abraded by the pessary and possibly may be infected. This is due to menopausal stenosis of the upper vagina, and to some diminution in thickness and health of the vaginal mucosa.

The following is a synopsis of the accepted changes in the genital tract at the menopause:

Ovaries: Smaller; follicles but no ovulation, later very atrophic, no follicles.

Uterus: Smaller; endometrium follicular type, later atrophic.

Cervix: Smaller usually, gland secretes less mucus.

Fornices: Usually shallow. This is accentuated by shrinking of cervix.

Vagina: Constriction ring possibly, in lower vagina. Mucosa may become thin.

Urethral orifice: May show prolapse of mucosa, which is seldom tender as in true caruncle.

External Genitalia: Labia minora may be atrophic.

Fallopian Tubes: These have not so far been studied, But probably join in the general shrinking process.

The histology of the vaginal mucosa, after the menopause is not agreed upon by the authorities. Murray (38) and others (41), (42), (29), (21) have shown that a modified cycle of growth and desquamation occurs in castrated rodents. In the menopausal woman a variety of views is met in the literature. Papinicolau and Shorr (17), (20) are undecided about the condition of the vagina, while Schultheiss (44) notes the maintenance of the normal sexual adult picture for years after radium or surgical castration. Murray (38) believes that the changes of the mucosa are most marked in old women.

In short, as in the normal adult woman, the histology and physiology of the vaginal mucosa is still very doubtful.

SCOPE OF THE INVESTIGATION.

There were investigated 315 cases:-

Normal	13
Normal Post-menopausal	84
Radium Menopause	100
Menopause after hysterectomy or surgical castration	118

The scope of the investigation is outlined in the following case-sheet. All the subjective findings have been disregarded except flushing, owing to obvious errors and inaccuracies. For instance, the gleaning of facts on the sex-life of an elderly Aberdeenshire woman proved not only exhausting to both patient and investigator, but practically devoid of value.

Specimen Case Sheet.

MENOPAUSAL FOLLOW-UP CLINIC.

Name: Mrs. D.

Case No: 339. Present Age: 46. Para: 3.

Disease: Non-malignant Uterine Haemorrhage.

Radium on: 31.6.37. (50 mgm. x 48 hours).

Last bleeding P.V.: 31.6.37.

Menopausal Symptoms before Radium:

Flushings for one year on occasions, mild.

Headaches for one year on two days each month.

THE MENOPAUSE.

Date:	1.3.39.	2.4.39.
Increased Weight:	Nil.	
Flushings:	Severe.	Nil.
Nervousness: Before:	Nil.	
After:	Nil.	Nil.
Best in Heat or Cold:	Doubtful.	Doubtful.
Headache: Before Ra:	Present.	
After Ra:	Worse, every 2nd day.	Nil.
Libido: Before:	Good.	
After:	Nil.	Nil.
Frequency of Intercourse: Before:	Weekly.	
After:	Every 6 to 8 weeks.	None attempted. (Biopsy).
Dyspareunia (Type): Before:	Nil.	
After:	Nil.	
Orgasm: Before:	Occasionally.	
After:	None.	
Pruritus: Before:	Nil.	
After:	Slight (nocte).	
Discharge: Before:	Nil.	
After:	Nil.	
Vulvitis:	Nil.	
Urinary Symptoms: Before:	Frequent attacks of cystitis.	
After:	None.	
Bowels:	Regular.	

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C. CHANGES IN THE GENITAL TRACT IN THE MENOPAUSE.

It will be shown later that marked changes of the anatomy of the genital tract become more common in the older menopausal women, although the individual degree of change may vary strikingly from case to case. For example, a menopausal woman of 48 with a tensile roomy upper vagina may manage to wear a ring pessary for a slight prolapse in comfort. At 68 however, two difficulties arise: (a) she may not manage even a small pessary into the fornices, and (b) if she does manage, the mucosa is easily abraded by the pessary and possibly may be infected. This is due to menopausal stenosis of the upper vagina, and to some diminution in thickness and health of the vaginal mucosa.

The following is a synopsis of the accepted changes in the genital tract at the menopause:

Ovaries: Smaller; follicles but no ovulation, later very atrophic, no follicles.

Uterus: Smaller; endometrium follicular type, later atrophic.

Cervix: Smaller usually, gland secretes less mucus.

Fornices: Usually shallow. This is accentuated by shrinking of cervix.

Vagina: Constriction ring possibly, in lower vagina. Mucosa may become thin.

Urethral orifice: May show prolapse of mucosa, which is seldom tender as in true caruncle.

External Genitalia: Labia minora may be atrophic.

Fallopian Tubes: These have not so far been studied, But probably join in the general shrinking process.

The histology of the vaginal mucosa, after the menopause is not agreed upon by the authorities. Murray (38) and others (41), (42), (29), (21) have shown that a modified cycle of growth and desquamation occurs in castrated rodents. In the menopausal woman a variety of views is met in the literature. Papinicolau and Shorr (17), (20) are undecided about the condition of the vagina, while Schultheiss (44) notes the maintenance of the normal sexual adult picture for years after radium or surgical castration. Murray (38) believes that the changes of the mucosa are most marked in old women.

In short, as in the normal adult woman, the histology and physiology of the vaginal mucosa is still very doubtful.

SCOPE OF THE INVESTIGATION.

There were investigated 315 cases:-

Normal	13
Normal Post-menopausal	84
Radium Menopause	100
Menopause after hysterectomy or surgical castration	118

The scope of the investigation is outlined in the following case-sheet. All the subjective findings have been disregarded except flushing, owing to obvious errors and inaccuracies. For instance, the gleaning of facts on the sex-life of an elderly Aberdeenshire woman proved not only exhausting to both patient and investigator, but practically devoid of value.

THE MENOPAUSE.

Date:	1.3.39.	2.4.39.
Increased Weight:	Nil.	
Flushings:	Severe.	Nil.
Nervousness: Before:	Nil.	
After:	Nil.	Nil.
Best in Heat or Cold:	Doubtful.	Doubtful.
Headache: Before Ra:	Present.	
After Ra:	Worse, every 2nd day.	Nil.
Libido: Before:	Good.	
After:	Nil.	Nil.
Frequency of Intercourse: Before:	Weekly.	
After:	Every 6 to 8 weeks.	None attempted. (Biopsy).
Dyspareunia (Type): Before:	Nil.	
After:	Nil.	
Orgasm: Before:	Occasionally.	
After:	None.	
Pruritus: Before:	Nil.	
After:	Slight (nocte).	
Discharge: Before:	Nil.	
After:	Nil.	
Vulvitis:	Nil.	
Urinary Symptoms: Before:	Frequent attacks of cystitis.	
After:	None.	
Bowels:	Regular.	

EXAMINATION.

Date:	1.3.39.	2.4.39 (Oestrin).
General Make-up:	Good.	
Heart:	N.A.D.	
Lungs:	N.A.D.	
B.P.:	140/90 mm.	
Breasts:	No change.	Tingling felt occasionally.
Nipples:	Normal. Not erectile.	Erectile ? Larger.
Hair:	No colour change.	
Abdomen:	Normal.	

PELVIC EXAMINATION.

External Genitalia:	L.Labium hypertrophied ++.	
Vaginal Mucosa:	Red and spotted. Bled on examination.	Healthy, wrinkled.
Cervix:	Small. No mucus. Sound did not pass.	Enlarged +. Sound passed 3". Mucus +.
Fornices:	Closed: No constriction ring.	Definitely deepened.
Uterus:	Not made out.	Appears normal in size.
Urethral Orifice:	Normal.	
Trigone:	Normal.	

BIOLOGY of the VAGINA.

Date:	1. 3. 39.	2. 4.39 (Oestrin).
Secretion:	Fair amount.	Abundant.
Appearance:	Whitish-green.	White.
pH:	5.4	4.2
Wet-Drop:	Pus, Squames, No Trichomonas.	Squames.
	VAGINAL SMEAR.	
Papinicolau Stain:		
Mucus:	Nil.	Nil seen.
Preponderant Cell:	Nucleated squames.	Nucleated squames.
Deep Cells:	V. occasional.	Nil.
Typical Cornification:	Moderate.	Moderate.
R.B.C.	Nil.	Nil.
W.B.C.	+	Nil.
Classified:	III.	III.
Gram Stain:	Doderlein B ++, B.coli ++.	Pure Doderlein.
	HISTOLOGY.	
	Normal sexually mature 3-layered type. Superficial layer, 8 cells thick. Stratum spinosum 15 layers, St. germinativum, single. No foci of infiltration. 300 u thick.	No Biopsy.
Glycogen:	Moderate amount.	
Uterus:	No biopsy taken.	

Urinary Oestrin:
(48 hours). Not done.

Treatment & Follow-up:

1st March, 1939: Stilboestrol mgm.1 with food daily;
Total 28 mgm.
(28 x 25,000 I.U.Oestradiol Benzoate).

2nd April, 1939: Reported: No nausea or sickness.
Much improved (see above).
Stilboestrol discontinued.

Chapter 3.

METHODS OF EXAMINATION.

The genitalia were examined carefully, and the vaginal secretion obtained at the same time by means of a blunt edged spoon which could be kept in a test tube (in a similar manner to a throat swab). The secretion was gently rubbed off the lateral vaginal wall, but occasionally obvious cervical secretion was included. The secretion was examined for the Trichomonas Vaginalis on a "wet-drop". Papinicolau's technique (16), although laborious, provided excellent smears for photomicrographs and was usually adopted, although in the latter part of the investigation Gram's stain proved itself to be quite adequate. The bacteriology was not extensively followed out. In several cases culture was done, but usually a (Gram's) stained film sufficed. The pH was estimated by B.D.H. Colorimetric method; if the secretion were scanty or blood-stained, e.g. in the elderly menopausal group, no reading could be obtained. A biopsy of vaginal epithelium was taken from the posterior vaginal wall about 2" from the introitus. The method used was to insert a Cusco's speculum and turning it laterally, allow a bulge of posterior vaginal wall to protrude between the two blades of the speculum. Large toothed dissection forceps

were used to raise a piece of epithelium and a circular piece of epithelium about ½" x ¼" was cut cleanly with a new blade in a Bard-Parker scalpel. No anaesthetic or antiseptic was used, and if the knife were sharp, little pain was felt by the patient. A sterile pad of gauze was inserted and held in position while the speculum was removed. This technique of taking biopsies has been satisfactory. In only two cases was there severe bleeding - in both these cases the anterior wall had been used, and histologically it was obvious how much more vascular this tissue was in comparison to that of the posterior wall. One case of vaginitis followed a biopsy in a post-menopausal case, but quickly cleared up under oestrin therapy.

The fixative used was Picric-Dioxane, but Pick's solution was used when glycogen was not being stained. The method used for staining of glycogen was that of Best modified by Carleton (58).

Salmon & Frank's (51) classification of vaginal smears was adopted in the first place, but was not entirely satisfactory. They divided smears into four grades as follows:-

Grade IV = Flat squames with small or no nuclei.
" III = Flat squames with occasional pus cells.
" II = Flat squames, compact or deep cells, pus.
" I = Leucocytes +++, oval shaped cells with large nuclei.

The weakness of this classification lies in its dependence on the size of the squame. If it be slightly smaller than normal and with a larger nucleus than usual, that may come from a thin epithelium whose most superficial layer is a somewhat flattened stratum spinosum cell, i.e. a more or less senile epithelium. Secondly, 13 of our smears showed deep cells and no pus and could not be classified by this method. In consequence we have attempted to work out a method of reading smears, the details of which follow.

A series of vaginal smears and corresponding epithelium were compared. The epithelium was measured with an eyepiece micrometer. The average of six readings being taken in all cases, to compensate for the variety of thicknesses obvious even in a small area of epithelium.

The variable observations were:-

1. Differentiation into layers.
2. The thickness of the epithelium.
3. The presence or absence of round cell infiltration of the submucosa (Lamina Proprium).

There were four types of epithelium.

(a). <u>3 layered type</u> with 1. Flat keratinised superficial layer.

2. Intermediate stratum spinosum cell layer.
3. Basal stratum germinativum layer.
4. Rarely, accumulations of round cells in lamina proprium.

(b). 2 layered type: 1. Stratum spinosum cells with possibly some degree of flattening superficially.

2. Stratum germinativum cell layer.

3. Round cell accumulation of L. proprium, occasionally.

(c). Undifferentiated type: Several layers of cells not different in appearance from the basal (germinativum) layer.

(d). "Combined type": Where areas like (a) and (b) and (c) were present in the length of the biopsy.

Classification of any epithelium according to the degree of differentiation was a hopeless proposition since all three layers could be present in obviously senile tissue. Moreover, in a great many cases called "2 layered type" the thickness of the epithelium was well within normal limits. Accordingly, a classification is presented based on the thickness of the tissue rather than on the degree of differentiation.

	Diff^{n}. into layers.	Minimum Thickness.	Average Thickness.	R.C. Infilt^{n}.
Adult Epithelium:- Figs. 10, 11, 11A.	(a) 3 layered type +++. or (b) 2 layered type.	* 175 u.	274 u.	Rare.
Moderately Senile Epithelium:- Fig. 12.	3 or 2 layered type.	100 u.	146 u.	Occ.
Senile Epithelium:- Fig. 13.	Undifferentiated type.	-	86.4 u.	Usual.
"Combined" type:- Fig. 14.	Senile + differentiated areas.	-	-	Occ.

Bloom gives 200 u for the average thickness of normal (sexually mature) epithelium. The variety from case to case, in this menopausal series, is great, some reaching 550 u in thickness. 142 cases with artificially induced menopause were examined and the results of classifying them as above were:-

		%age.
Normal (2 or 3 layered differentiated type)	= 121	85.2
Mod. Senile	= 14	9.8
Senile	= 4	2.8
"Combined" type	= 3	3.1

The following photographs show examples of each type of epithelium defined in the above chart.

---

* u = $\frac{1}{1000}$ mm.

Fig. 10. Normal Epithelium.

Mrs. S., aged 40. Radium Menopause 2 years ago.

Vaginal biopsy shows normal 3-layered adult epithelium with much glycogen in the superficial layer (S). The other two layers are stratum spinosum (Sp.) and stratum germinativum (G.). Average thickness 418 u. Best's Stain X 130.

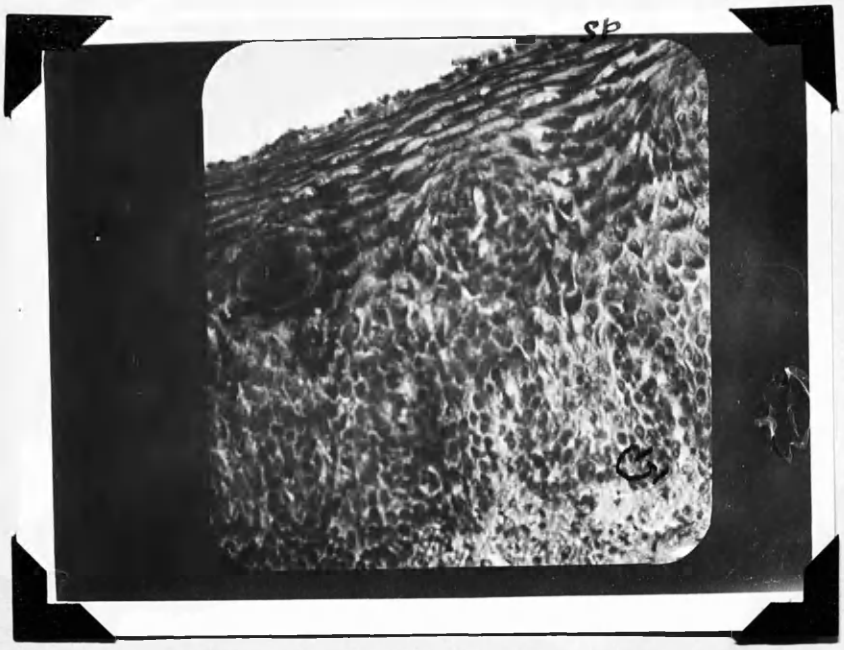

Fig. 11. Normal 2-layered Epithelium.

Mrs. H. aged 73. Spontaneous Menopause at 55.

2-layered adult epithelium 340 u thick; glycogen abundant. Superficial stratum spinosum cells (Sp.) are slightly flattened but differ from the keratinised flat layer of fig. 10. G. = Stratum germinativum.

Best's stain X 215.

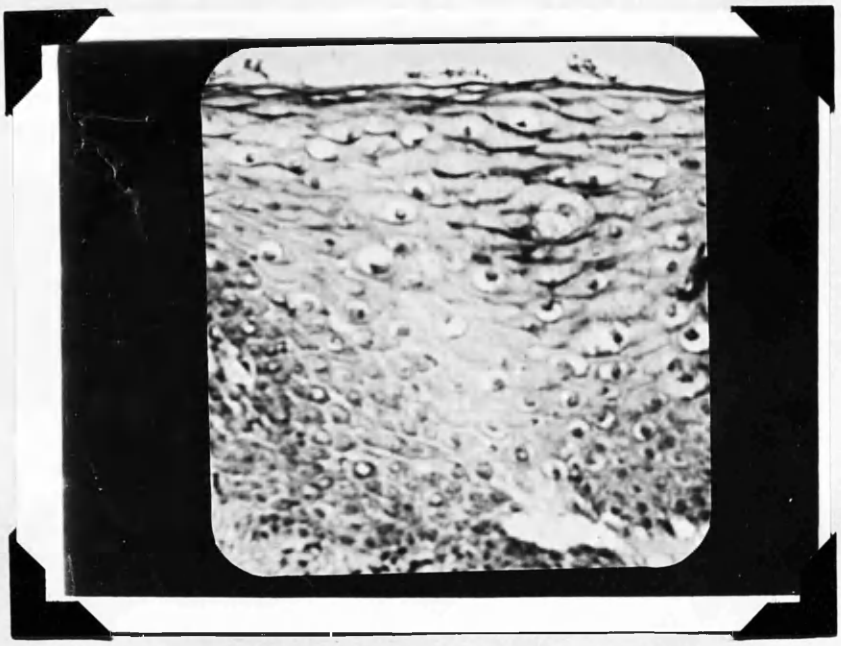

Fig. 11A. 2-layered Normal Epithelium.

Mrs. E. aged 50. Spontaneous menopause at 42.

Stratum spinosum cells are slightly flattened superficially. Average thickness 250 u.

Best's stain X 215.

Fig. 12. Moderately Senile Epithelium.

Mrs. C. aged 47. Radium menopause at 46.

3 layers can be defined, viz: Stratum germinativum (G), Stratum spinosum (Sp.) and flat superficial layer (S). The average thickness was less than 175 u, so that it was classified as moderately senile despite its differentiation into layers.

Best's stain X 215.

Fig. 13. Senile Epithelium.

Mrs. C. aged 47. Radium Menopause at 45.

No differentiation except for one layer of slightly flattened superficial cells. Note lymphocytic infiltration of Lamina proprium (L). Average thickness under 100 u.

Best's stain X 215.

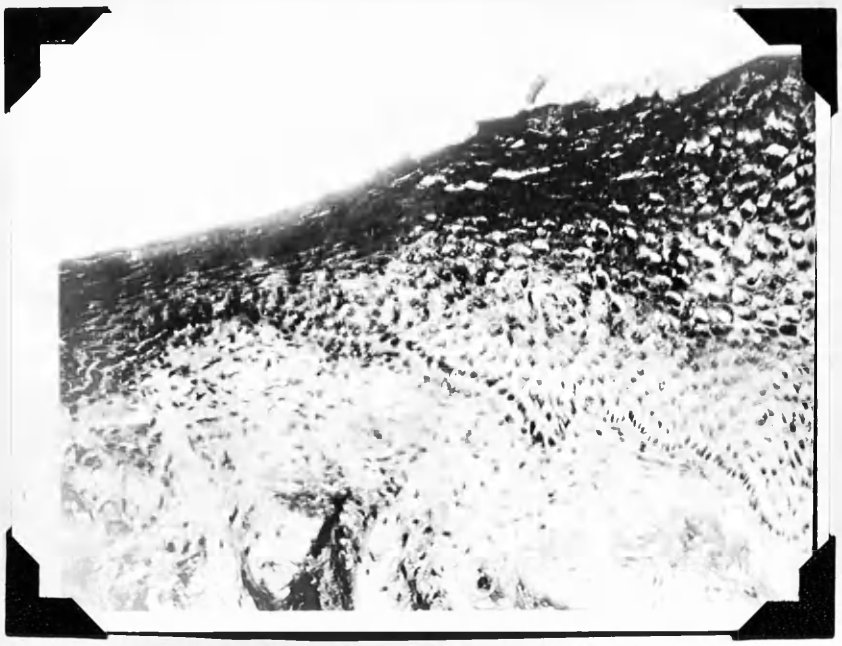

Fig. 14. "Combined" type of Epithelium.

Mrs. S. aged 50. Spontaneous Menopause at 47.

The Lamina proprium approaches the epithelial surface at areas causing patchy areas of definitely senile thickness (60 u thick). Smears from this type of epithelium provide a mixture of cells of varying maturity.

Best's stain X 215.

The Significance of Vaginal Smears.

Vaginal smears are commonly used as an index of the effect of oestrin on castrated mice, and have been advocated for estimating the full effect of oestrin on menopausal women. It is important to know if, by looking at the surface cells a gauge is thereby obtained of the underlying epithelium.

138 smears of vaginal mucosa were correlated with biopsies. The usual surface cells were flat squames, and occasionally they were no more than slightly flattened stratum spinosum cells. The mean of the maximum length of six of these cells (which predominated) was taken; and on the average in this series proved to be 55 u, but 66 u down to 40 u were included as normal. If the slightly flattened stratum spinosum cell under 40 u predominated, the smear was classified as Grade II, as were those smears in which globular and more typical stratum spinosum cell predominated.

Classification of Smears.

	Squames over 40 u	Stratum spinosum cells (possibly flattened).	S.germinativum cells.	Leukocytes.	Type of Epith. expected.
Grade III (Figs.15 & 16).	++	occ.	v.occ.	±	3 or 2 layered over 175 u thick. i.e. Normal.
Grade II (Fig.17).	+	+++	occ.	±	3 or 2 layered over 100 u thick. i.e. Mod. senile.
Grade I (Fig.18).	-	occ.	+	±	Undifferentiated under 100 u. i.e. Senile.
(Combined Type). (Fig.19).	++	++	++	±	Senile with normal areas.

Examples of each of this group follow:

Fig. 15. Normal Smear Grade III.

Mrs. H. Aged 88 years. Spontaneous Menopause 40 years ago.

Smear shows flat squames with small nuclei. No pus. Average length of squames = over 40 u. Biopsy confirmed the normality of the epithelium which was 200 u thick, and well differentiated into 3 layers. Gram's Stain x 215.

Fig. 16. Grade III Smear.

Mrs. A. aged 42 years. Hysterectomy and Unilateral Salpingo-oophorectomy at 40.

Smear shows flat squames with small deeply stained nuclei. No pus.

Biopsy proved the epithelium to be normal with rather more lymphocytes in the submucosa than normal.

Papinicolau stain X 215.

Fig. 17. Grade II Smear.

Mrs. F. aged 41. Hysterectomy + Bilateral Salpingo-oophorectomy at 40.

Smear shows small cells rather flattened (S.spinosum) but no pus. Papinicolau stain X 224.

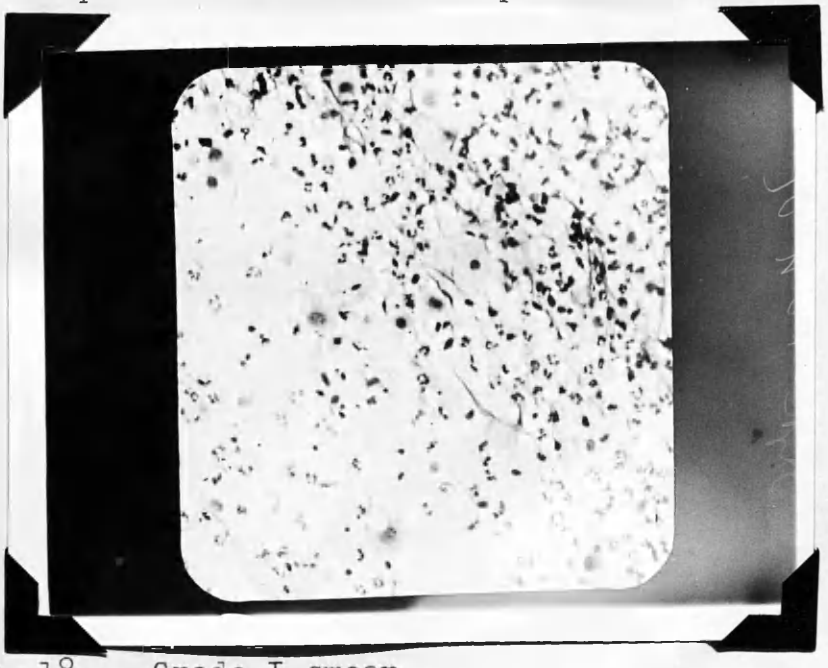

Fig. 18. Grade I smear.

Mrs. C. aged 45. Radium Menopause at 43.

Smear shows deep cells and pus. Biopsy confirmed the senility of the smear. Papinicolau stain X 224.

Fig. 19. Combined type.

Mrs. S. aged 50. Spontaneous Menopause at 47.

Both large squames (L) and smaller deep cells (D) are seen. The type of epithelium proved to be of combined type (Fig.14) with patches of senile epithelium.

Gram's stain X 215.

The correlation of Epithelium with smear was not satisfactory except in Grade III, where in 118 cases 108 or 91.5% proved to have forecast accurately the presence of normal epithelium. The ten Grade III smears which did not correspond to the underlying epithelium had predominantly squames over 40 u; the underlying epithelium proved to be in all cases definitely of senile type of less than 175 u thickness. Grade II, however, gave quite unsatisfactory forecasts of the underlying epithelium. Of Grade II there were twelve cases, nine of which proved to have quite normal 3 or 2 layered epithelium. Three smears were from moderately senile epithelium, i.e. corresponded to the histology. Grade I (undifferentiated small cells) came from the epithelium anticipated in two out of four cases. The "combined" type of smear represents one of the difficult types of smear to read; all varieties of cells exist, squames over 60 u in length and small cells too, in about equal numbers. Only in two out of four cases was the "combined" type of epithelium forecasted accurately.

It will be obvious that only smears with flat squames can be "read" with accuracy. The so-called "negative" smears (II - I etc.) can give no forecast of the differentiated state or thickness of the underlying epithelium. Neither can vaginitis be diagnosed from a smear, a point which will be elaborated later.

Chapter 4.

THE NORMAL MENOPAUSE.

Material.

84 cases were examined. The cases were drawn mainly from surgical wards, cases of fractures, renal calculus, etc. Debilitated patients were excluded.

Investigation regarding the severity of flushing before and after the cessation of menses was carried out. The pelvic examination, smears of vagina, etc. were done as in the case-sheet. (Page 20).

The average age of 84 patients examined was 63 years, but they varied from 40 to 88 years old. The average onset of the menopause was (in 65 cases) 45.3 years, the youngest being 35 and the oldest 55. It will be noted that 18 cases had doubt about the date of the menopause.

The Incidence of Flushing. (84 cases).

Before onset of Menopause	Nil.	37	50%
	Mild	30	50%
	Mod. severe	6	
	Severe	1	
	Doubt	10	
After onset of Menopause	Nil.	24	30.8%
	Mild	41	52.6%
	Mod. severe	10	12.7%
	Severe	3	4%
	Doubt	6	

The patients were carefully questioned (always by myself) and on ten occasions the information was judged unreliable. The grading of the severity of flushing was:-

Mild: Occasional flushes, no discomfort. No disturbance of sleep.

Moderately Severe: Occurring several times daily. Discomfort and sweating with flushes, occasionally causing patient to waken from sleep.

Severe: Frequent hot flushes. Insomnia marked because of flushes with sweating. Hormonal or other therapy sought for relief.

(a). Flushing before the Menopause.

The climacteric has been defined as a wider term than the menopause, but the above results suggest that the amenorrhoea is part of the same change in the hormono-poietic system which, before the menopause, causes flushing. In 37 or 50% of the cases, flushing was noted before the menopause, in seven (9.4%), it was a serious complaint. Cessation of periods in a woman with mild pre-menopausal symptoms usually leads to an exacerbation of those symptoms. It is interesting to note that in the seven cases who had severe pre-menopausal flushing five were improved after the onset of amenorrhoea, two were not improved. This is difficult to explain in the light of Whitehouse's (68) view that women at the climacteric will have no flushing if they have a period.

(b). Flushing after the Menopause.

In this series, 78 were interviewed and six were discarded as doubtful. 65 (83.4%) appeared to have none or only mild flushing. Moderately severe flushing occurred in 13 cases (12.8%) and severe flushing in three cases (4.8%). So that 13 or 16% in total, were upset seriously by the "change of life", a fact which must be remembered when estimating the ill-effects of an induced menopause.

The Council of the Medical Women's Federation (61) investigated 1000 normal women after the menopause, and found that 62.3 per cent had flushings of varied intensity. This figure is only slightly lower than in this small series where 70% were affected by flushing.

CHANGES in the GENITALIA after the NORMAL MENOPAUSE.

(a). External Genitalia.

66 cases were examined; the extent of the examination was in most cases carried out with speculum and finger in the usual fashion, but the uterus was not felt in the majority of cases. In nine cases a definite degree of prolapse was present, but the patients had no symptoms and required no treatment. The following terms are defined:-

Normal Genitalia: No evidence of inflammation or atrophy of labia.

Vulvitis: Vulva red, inflamed and possibly sodden.

Atrophy of Labia Minora: Variable degree of atrophy up to almost complete absence.

In no case was kraurosis seen, but leukoplakic changes were present in two cases - aged 77 and 65 respectively. In neither was the necessary histological confirmation possible and the diagnosis rests purely on the clinical appearances.

Wide differences in the degree of atrophy were met. 43 (65.2%) of the cases were graded as normal. The average age of this group of normal cases was 60. 16 (24.2%) showed a variable degree of atrophy of the labia minora, while 7 (10.6%) showed definite vulvitis. The average age of those with atrophic labia minora was 69. While those with vulvitis averaged 69 also, indicating that the incidence of these changes is more common late in the menopause.

(b). Vaginal Findings.

There were 11 (18.9%) cases whose vaginae and external genitalia appeared normal. The average age was 54 years, the oldest being 76 years.

It is of interest to note normal conditions of the genitalia after cessation of menses, for it tends to confirm the presence of adequate oestrin in the circulation. As an example, Case 027 was 76 years old, had the menopause 23 years before, yet showed quite normal genitalia with deep fornices and a large mucus-secreting cervix. She had had no symptoms at the climacteric.

Attention was paid to the following points:-

	Normal.	Menopausal or Pathological.
Introitus:	Soft, moist, not stenosed.	Burnished; fissured, leukoplakia, stenosed.
Urethra:	Slit like.	At meatus caruncular tissue, red, oocasionally tender.
Mucosa:	Bluish-red, rugosae present.	a) Smooth pale but healthy. b) Smooth: Red spots. c) Tendency to peel and bleed on examination.
Cervix:	Fair size, Mucus secretion.	Atrophic - possibly even absent.
Fornices:	Deep laterally.	Flattened - this accentuated by accompanying cervical atrophy.
Constriction Band in Vagina:	Absent.	Present: About 3" from introitus.
Closure of Upper Vagina:	Absent.	Present - further stage of constriction band.
Uterus:	Normal size.	Atrophic - diminished in size.

Vaginal Findings in 58 cases.

	No.		Percentage.	
Normal	11		18.9	
Urethral Caruncle	10		17.2	
Abnormal Mucosa	29		58.6	
Cx. small F. flat	27	36	45.2	60.7
Fx. flat alone	9		15.5	

(Many of these findings were duplicated in each case.)

Of the 58 cases examined in detail per vaginam, 47 (80.7%) showed a variable degree of change following the menopause. The "caruncle" defined above is worthy of mention since most text-books look on it as abnormal. It was seen in ten cases. The red tissue at the meatus was not tender and it was continuous with urethral mucosa. It did not bleed on touching.

The mucosa looked abnormal in 29 cases (58.6%), 14 being classified as "pale and smooth", 15 as smooth and studded with red punctate areas. These mucosal findings will be correlated later with the histology, but it was common to meet apparent vaginitis which was not confirmed histologically. These variations from normal are significant when elderly women are under investigation for suspected vaginitis, for it appears that quite definite vaginitis clinically may frequently be no more than a variation from the normal menopausal appearance. (See chapter 7).

Closure of the fornices with a variable but definite atrophy of the cervix was present in 27 cases (57.7%), while closing of the fornices without cervical atrophy was noted in nine cases (19.1%). Obviously the smaller the cervix the more accentuated the flattening of the fornices appeared. This closing in of the upper vault is apparently due to an increasing denseness of the parametrium which contracts down after the menopause.

In the radium group a constricting band in the vagina was occasionally noted about 3" from the introitus, quite apart from the fornices, and probably was part of the same shrinking process. In the normal group, complete closure of the vagina by such a circular band occurred in two cases aged 88 and 67 respectively; the stenosis was about 2" from the introitus. The action of oestrin on these bands and on the fornix and lower vagina is dramatic; softening of the contracting tissue is followed by deepening of the fornices and, to accentuate this, the cervix increases three or four times in bulk and length. This is highly suggestive that the menopausal changes are due to inadequate oestrin in the circulation for replacement of oestrin will lead to a resumption of the previous state.

Age - Genitalia Correlation.

	Ext. Genitalia.		Vagina and Cervix.	
Age.	Normal.	(1) Abnormal.	Normal.	(2) Abnormal.
35-55	13	2	8	4
56-65	17	3	1	15
66-88	12	18	1	26

(1). = Atrophic minora, or vulvitis.

(2). = Mucosa abnormal (or) and flat fornix, small cervix, etc.

The older type of patient (over 66 years) appears to show more marked atrophy of the genitalia than the

younger, and this is more marked in the vagina where 26 out of 27 (93%) showed some senile change (fornices, cervix, etc.). The 56-65 group, although showing little gross vulvar change, presented senile changes in the vagina in 15 out of 16 cases (94%). The 35-55 or younger group showed senile vaginal changes in four out of eight cases. It would appear therefore that the first part of the genital tract to show senile changes is <u>in</u> the vagina, at the fornices, cervix, etc., and that this is found in almost every case over 56 years. The external genitalia showed definite senile changes, but only in the group aged 66 or more was a notable percentage of cases affected (viz. 12 out of 18).

<u>Summary of Changes in the Genitalia</u>: In 11 cases only (18.9%) no genital changes were noted, their average age was 54.

In 43 (65.2%) no changes in the external genitalia were noted, their average age being 60 years.

In the remaining 23 (34.8%) the labia minora were atrophied in 16, vulvitis was present in seven. The average age in this group was 69.

47 (80.7%) of cases showed some vaginal change as shown on page 43.

Apparently the changes <u>in</u> the vagina occur earlier in the menopause than do changes of the external genitalia.

DETAILED STUDY of the VAGINA.

(a). Vaginal pH.

The method used was accurate enough for the purpose, namely, the B.D.H. Colorimetric technique.

Results:

4.9 or less	4 cases	(8%)
5 to 6	9 "	(18%)
Over 6	37 "	(74%)
Total No. of cases	50	

Analysis of the four cases in whom the vaginal secretion was acid showed that their ages vary considerably, viz: 47, 61, 64 and 73 years. These cases were further examined and in each case Grade III (normal) smear was obtained. Two cases were examined histologically and normal epithelium was seen. Pure Doderlein Bacilli were present in three, while one had mixed organisms. So that in these four cases, the other findings tally with the low pH obtained.

46, or 92% were relatively more alkaline. The reason for the high incidence of raised pH is certainly not because of excessive cervical mucus, for the cervix is usually atrophic and less active in the menopause. It is most likely that less epithelium (with glycogen) is desquamated, so that the enzymes normally present to break down carbohydrate to lactic acid have less material

to act on. This fact is, moreover, dependent on the ovaries; it is a striking fact that the administration of oestrin to a menopausal woman will lower the vaginal pH rapidly, and it seems to do so by thickening the mucosa and increasing the amount of cells shed into the lumen of the vagina.

(b). Bacteriology.

The extent of the investigation was simply to stain vaginal smears by Gram's Iodine Method and examine several fields (under oil immersion). Great variation in the shape of the Doderlein Bacillus was encountered. Occasionally long thread-like organisms were seen (not unlike yeasts, but without budding); possibly the full length of the organism was not stained Gram positive, but maintained a pink colour. Again the Doderlein Bacilli might be short and almost coccal in form, and if a culture were made, pure long bacillus of Acidophilus type (Doderlein) would be obtained. Smears were graded into four groups:-

(1). Pure: Only Döderlein B.

(2). Almost Pure: Döderlein B. with very scanty B. coli or Gram -ve cocci, etc.

(3). Mixed: Mixture of Gram +ve and -ve organisms, usually including some Gram +ve organisms taken to be B. Döderlein.

(4). Occasional Cocci: Scanty Gram +ve cocci.

Results:

Total number of Cases 60

Pure, or almost Pure Dod. B. ... 17 (28.3%)

Mixed B. 32 (53.3%)

Occ. cocci 11 (18.3%)

(Trichomonas Vaginalis + Mixed B. 3).

The first fact, that 17 (28.3%) out of a comparatively small series showed a normal flora, is contrary to the usual text-book opinion; even Davis & Pearl (Chart p. 2) state that sparse bacilli and occasional cocci are to be found after the menopause.

The age of these patients with normal flora varied from 88 to 47 years, (7 cases were actually over 70) so that, no relationship between the patient's age and flora is evident. All 17 cases had normal, Grade III smears, and on examining the mucosa of six cases, three showed normal histology; the remaining three were of "combined type", i.e. showing alternate senile and normal areas. Nevertheless, no really senile tissue was found to have normal flora on it, and with the fact that 17 normal smears were obtained, it may be suggested that the B. Doderlein depends on a more or less normal mucosa to favour its growth and reproduction.

Thirteen of the cases with normal flora had pH estimations of over 4.9, three were less than 4.9 and

one was doubtful, so that the presence of normal flora in the vagina of post-menopausal women does not necessarily coincide with normal acidity (i.e. less than a pH of 5).

(c). Vaginal Smears.

59 cases were examined; the value of Grade III smears in forecasting, fairly accurately, normal epithelium has been discussed.

Results: Grade III ..... 47 78%.
Grade II ..... 8 14%.
Grade I ..... 4 7%.

The high incidence (78%) of normal smears in this menopausal group supports the bacteriological and pH findings in pointing to the presence of oestrin or some similar hormone which must persist in amounts sufficient to maintain the health of the vagina in a high proportion of women for many years after the menopause.

Age:	50 or less.	51-60 years.	61-70 years.	70 and over.
Smear Grade I ..	1	1	2	-
II ..	0	2	4	2
III ..	6	13	13	15
Total Smears ...	7	16	19	17

Correlation of the vaginal smear with the patient's age shows that the normal smears are spread evenly over the patients of various age. The fact that 15 out of 17

patients over 70 years of age provided normal smears is noteworthy.

(d). Vaginal Epithelium.

Results:

Total number of biopsies 23

Normal epithelium 15 (65.2%)

Moderately senile 4 (17.4%)

Combined Type (Senile in areas only) 4 (17.4%)

Classified according to Ages:

Age:	50 & under.	51-60 years.	61-70 years.	70 & over.
Epith. Adult	2	4	3	6
Epith. Mod. Senile ..	1	1	1	1
Combined Type	1	2	0	1
Total Biopsies	4	7	4	8

15 (65.2%) of the cases proved to have normal epithelium. Classification according to age group again shows that the old patients as well as the younger group have a good proportion of normal epithelium. e.g. of eight biopsies taken from women over 70, six showed normal epithelium, a fact which agrees with the other vaginal findings.

SUMMARY OF THE NORMAL MENOPAUSE.

(1). 84 cases were examined subjectively and objectively. Flushing occurred in 37 (50%) of cases before the menopause, but only in marked degree in 7 (9.4%).

Flushing after the menopause was absent or mild in 65 (83.4%) and severe or moderately severe in 13 cases (16%).

(2). The external genitalia show great variety from case to case, but in general the older cases show marked atrophy. The vagina shows senile changes earlier than the external genitalia.

(3). Vaginal Investigation: (a). The pH of the vagina is usually alkaline in the menopause with, however, exceptions, e.g. four cases under 4.9 out of a total of 50).

(b). Bacteriology. 17 (28.3%) had pure or almost pure Döderlein Bacilli, seven cases actually over 70 years of age.

(c). Vaginal Cell Smears. 47 or 78% had normal Grade III smears, the cases being drawn evenly from the old or young age groups.

(d). Histology of Mucosa. 15 (65.2%) of biopsies proved normal, four were moderately senile and four showed "senility in areas" of the biopsy.

CONCLUSIONS.

From the foregoing figures it will be seen that the usual statement made that after the menopause the genital tract undergoes atrophy and the vaginal mucosa becomes thin, is far from representing the true state of affairs. In actual fact,histological examination of the

vagina shows that in 65% the appearances were normal and this corresponds roughly to the finding of Grade III smears in 78%. In 28% there was a pure growth of Doderlein Bacillus and in 8% a secretion with a pH of less than 5.

One must conclude therefore that in some women very little change in the anatomy or physiology of the vagina takes place after the menopause, except probably some rise in the pH of the vaginal secretion with an influx of other organisms in some cases. There is great individual variation which does not seem to depend to any great extent on the age of the patient.

Chapter 5.

To compare the manifestations of the menopause occurring normally with those seen where the menopause has been induced artificially, a series of 214 cases have been studied. They consist of the following:-

	Cases.	Average Age.
(a). Radium (at least 2200 mgm.hr.) ...	100	49 years.
(b). Hysterectomy + 2 ovaries removed .	39	45 "
(c). " + 1 ovary removed ...	36	41 "
(d). "	39	38 "
	214	

THE MENOPAUSE INDUCED BY RADIUM.

100 patients who had the menopause induced by Radium were studied along the lines outlined for normals. They are divided as follows, according to their present age.

40 years and under	10 cases.
45 " "	31 "
50 " "	36 "
Over 51 years	17 "
Radium given after normal menopause	6 "
Total.-	100 cases.

The dose given was at least 50 mgm. for 48 hours with two exceptions (vide infra). The duration of the artificial menopause was at least a year; two exceptions were included, one of three months' duration and one of nine months. Only three cases failed to cease menstruating after treatment and details of these are as follows:-

Case 1. Present age 42. Had irregular uterine haemorrhage; endometrium normal. On 4.7.37 given Radium 50 mg. for 48 hours. Twelve months amenorrhoea followed; no flushings but headaches with dizziness apparently came on every month. Libido, which had always been mild, practically disappeared. Intercourse at three or four weekly intervals. Her weight rose 28 lbs. in two years. After twelve months, menses occurred at four-weekly intervals, rather profuse and lasting seven days.
Examination: Generally quite fit, obese, B.P. 130/80. Genitalia normal except for slight but definite flattening of the fornices.
Smear: pH 4.6; Grade III; Pure Doderlein B. Epithelium of vagina normal. Uterine biopsy: Endometrium at early oestrin phase. The cervical canal was passed with ease by a punch curette without anaesthesia. (Note: attempts to take endometrial biopsies in other menopausal cases failed, owing to closure of the cervix.)

Case 2. August, 1936 (then 24 years old) had radium in sub-castration dose of 50 mgm. x 26 hours on account of severe and prolonged menorrhagia. Amenorrhoea followed. Seven months later, severe menstrual period for seven days, followed by a further eight months of amenorrhoea. She menstruated regularly on six occasions in 1938 without abnormal loss; also once in the four months preceding examination at our clinic in April, 1939.
Symptoms: Flushing: 1936. About twice weekly, hot flushes with sweating.
1937. Only at "period time" and absent if flow of blood came: since then very occasionally.
Pruritus: Very severe at night. Improved spontaneously after six months.

Leucorrhoea: Persistent yellow discharge. In hospital 1938 - no improvement. Still has to douche regularly because of this.

Hair: Ten days after radium she developed a grey streak 2" broad from her brow backwards. After five months she had appendicectomy and developed a large bald patch. In the last three years hair has resumed almost completely, its normal fair colour, except for one small streak of grey, which still persists.

Examination:-

Very thin. B.P. 145/70.

Genitalia: Normal.

Smear: (Douching 12 hours before). pH 5.5. No pus. Grade III. Mixed flora.

Histology: 3-layered adult type with some excessive round cell infiltration of submucosa. Taken as normal.

No uterine biopsy was possible.

Case 3. 1935. When 37 years of age had 50 mgm. Radium inserted into the uterus with one flat box of 37.5 mgm. across the outlet of the cervix for 24 hours, the indication being given as "Cervicitis". The discharge was cured and amenorrhoea followed for 15 months. Periods followed normally for two years, but a spontaneous menopause followed in 1939, and no menstruation had occurred for four months before her examination at this clinic.

Flushing: Entirely absent.

Examination: General condition normal.
Genitalia: Normal (apart from slight prolapse).
Smears: pH 6.2, Grade III, Mixed flora.
Histology: 3-layered epithelium. Average 300 u. thick. Glycogen abundant.

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The Action of Radium.

This is not settled finally; some believe that the ovarian tissue is damaged so that ovulation is inhibited and finally shrinking of the whole ovary is brought about; other authorities emphasise the scarification of the endometrium following Radium. L. Philips (67) surveys the evidence and writes: "It is reasonable to

(Chart I). INCIDENCE of FLUSHING.

	Before 40		41+		46+		51+		Normal.		Hyst. only.		Hyst. + 1 Ovary.		Hyst. + 2 Ovaries.	
A. Before the Menopause.				%age		%age		%age		%age		%age		%age		%age
Nil		-	21	65.6	16	41.0	11	61.0	37	50.0	31	88.6	23	69.7	31	75.6
Present		-	11	34.4	23	59.0	7	39.0	37	50.0	4	11.4	10	30.3	10	24.3
Doubtful		-		-		-		-	10	-		-		-	4	-
B. After the Menopause.																
Nil		-	4	12.89		-	1	5.9	24	30.7	13	36.1	19	57.6	5	11.6
		%age														
Mild	5	50.0	16	51.61	20	55.5	10	59.0	41	52.5	21	58.3	14	42.3	18	41.9
Mod.Severe	4	40.0	9	29.03	7	19.4	4	23.5	10	12.8	*1	2.8		-	11	25.6
Severe	1	10.0	2	6.45	9	25.0	2	11.7	3	4.0	+1	2.8		-	9	20.9
Doubtful		-		-		-		-	6			-		-	2	

* Flushings followed two years after operation.

+ Severe flushings followed hysterectomy at 56 years of age.

assume that this result (i.e. amenorrhoea) is obtained, at least mainly, by the action of the rays upon the ovaries". (67).

The effects of menopausal doses of Radium have been studied in regard to symptoms and genital changes. The facts collected here will assist the clinician in deciding whether surgical or Radium treatment should be selected in a case where either treatment would suffice. There is practically no mortality in Radium therapy against an operative mortality of about 2% in most clinics following hysterectomy. However, if hysterectomy (with conservation of ovarian tissue) is performed, it has been suggested that atrophy of the genitalia and serious symptoms of the menopause which follow Radium will be avoided. Just how severe is the Radium menopause? Is it worse in younger or in older women? How does it compare with the normal menopause? An attempt to answer these questions is made.

Flushing after menopausal doses of Radium.

The chart on the page opposite shows that in 41, or 47% of cases flushing occurred before the menopause. This must be considered when gauging the severity of symptoms following radium therapy. The fact that in ten cases under 40 years, no pre-menopausal flushing occurred, suggests that this type of case may be unduly sensitive to the sudden onset of flushing in the menopause

and therefore may complain more than a patient who has felt the flushing effect before.

(a). Absence of Flushing after Radium.

Group:	Ra.	Castrate.	Hyst.with Ov. tissue left.	Normal.
No:	5	5	32	24
%:	5.3	11.6	47.8	30.7

Total absence of flushing following Radium was rare, only 5 (5.3%) cases being observed, as compared to 24 (30.7%) after the normal menopause, and 32 or 47.0% after hysterectomy with conservation of ovarian tissue. If the cases free from flushing after Radium are included with those which had slight flushing useful facts are obtained:-

(b). Mild or no Flushings after Radium.

Group:	Ra.	Castrate.	Hyst.with Ov. tissue left.	Normal.
Cases:	94	93	68	78
Mild Flushing or none.	56	23	67	65
%age:	56.4	53.5	98.5	83.7

The absence of flushing or its presence in mild form was noted in roughly the same proportion in the radium (56%) and castrate groups (53%), but in a much higher proportion of the spontaneous (84%) and surgical cases with conservation of ovarian tissue (98%).

(c). Severe or Moderately Severe Flushings after Radium.

Hunter (50) does not state the severity of flushing in his series of 150 cases (who had menopausal dose of radium); he states that only 8.7% of his series had flushing of the face, truly a remarkably low figure.

The Council of the Medical Women's Federation (61) investigated 1000 normal women and found that 62.3% suffered from flushing in some degree, following the spontaneous onset of the menopause.

In our series 39 (43.6%) were seriously disturbed by flushing after Radium therapy. The comparison and contrast between the normal and induced menopause is tabulated below:

Group:	Ra.	Castrate.	Hyst.with Ov. tissue left.	Normal.
No.of cases	94	43	67	78
No.of Mod.Severe or Severe Flushing	39	20	1 (see below).	13
Percentage	43.6	46.5	1.5	16.8

The close comparison (44%and 47%) between the radium and castrate groups is of interest. Contrasting strongly with this high figure is the normal where 16.8% were disturbed, and in the cases of hysterectomy with conservation of ovarian tissue, where only 1.5% were seriously upset by flushing. It will be pointed out

later that in the last-named group additions must be allowed for in the total because of "delayed" menopausal symptoms which may appear at the time when the menopause would normally have been expected, had no surgical treatment been carried out.

It has been suggested by many clinicians that radium will not produce severe menopausal symptoms if reserved for use on older women, i.e. 46 or over. The incidence of flushing in this series (Chart I) is about the same in all groups under 50 (viz. 41%), but there is a slight fall in the incidence in those over 50 (viz. 35%), so that the menopausal symptoms after radium appear in roughly the same proportion in both the younger and older type of women.

CONCLUSIONS.

The incidence of severe or moderately severe flushing therefore, is about three times greater where the menopause is induced by Radium or surgical castration than when it occurs spontaneously. Hysterectomy with retention of ovarian tissue was followed by practically no severe flushing, in contrast to the Radium menopausal group. This would support those clinicians who favour hysterectomy with conservation of ovarian tissue; however with the discovery of cheaper ovarian hormone therapy this disadvantage of Radium will doubtless be offset to some extent.

The effect of Radium on Post-Menopausal Women.

There were eight cases in this group. The series is too small to prove anything, but the facts are perhaps worth recording.

The reasons given for radium therapy were, in three cases, cervical erosion; in two cases, cervical polyp; and in three cases, non-malignant uterine haemorrhage.

There were three cases who, until the administration of radium, had definite flushing of the face. Their ages were at the time of operation 63, 62, and 66. The effect of radium was to cure their symptoms, at least it may be said that the cessation of flushing coincided with the administration of radium.

Of the remaining four post-menopausal cases, two continued to have mild flushing, while two had never had flushing following the normal menopause and did not develop them after treatment. The cures brought about might have occurred spontaneously. Whitehouse (68) reports that on one occasion severe flushing followed hysterectomy in a patient under his care. He re-opened the abdomen, removed both ovaries, and the flushings ceased.

We have also encountered a similar paradoxical effect following castration.

Case 986. Aged 54. On 4.4.38 had hysterectomy and bilateral oophorectomy performed for irregular uterine bleeding. Flushing and sweating which had been marked before, disappeared at once after the operation.

The series, in total, is too small to be conclusive, but they make obvious the difficulties of finding a rational explanation for flushing.

GENITAL CHANGES AFTER THE RADIUM MENOPAUSE.

(a). External Genitalia.

In the normal menopause 16 (24%) of the series showed a degree of atrophic change of the labia minora (a further seven showed vulvitis). In the radium group 13 (13.2%) showed atrophic labial changes, but if the age factor is allowed for the figures will probably approximate, since the 16 normal menopausal cases average in age 69 years, while the radium group averaged only 49. The dependence on the advanced age of the patient was noted in the previous chapter, when it was seen that in the normal menopausal woman the external genitalia were atrophied in a high percentage of the older women, so that it may be that in the course of years a higher percentage of the radium group will show external genital atrophy.

(b). Stenosis of the Vagina.

The shrinking process of the vagina and cervix (here called "Stenosis") was occasionally augmented by a circular constricting band found about 3" from the introitus. Stenosis was encountered in 61 (67%) of the radium cases, against 33 (77%) of normal menopausal women.

(Chart 2). pH ESTIMATIONS.

	Radium.				Normal.	Hyst. only.	Hyst. + 1 Ovary.	Hyst. + 2 Ovaries.
	Before 40	41+	46+	51+				
4.2 or less	-	3	1	-	-	8	1	-
4.3 - 4.9	4	2	5	1	4	6	8	1
5 - 6	4	8	6	3	9	15	10	8
Over 6	1	16	20	15	37	4	10	24

Complete or almost complete occlusion of the vagina was noted in seven cases (8%), when a circular band of tissue forming an obstruction to the examining finger was found about 3" from the introitus. The duration of the menopause in these cases showing circular bands, varied from three months to five years; in the two cases in which complete occlusion had occurred, it was five years. The age in all seven cases was over 50. In contrast, only two cases had occlusive bands in the normal menopausal group, their ages being 67 and 88 respectively.

The possible etiology of these stenosing bands and of the closing of the fornices has been discussed. Oestrin therapy has the same softening effect on these bands as it has on the parametrium of the lateral fornices.

The lower incidence of stenosis of the vagina following radium compared to normal menopausal women is probably due to the age difference, the former averaging 49, the latter 63 years, i.e. the radium group, it is anticipated, will join in the atrophic process which becomes more marked as the menopause progresses.

The effect of vaginal stenosis on the patient is probably slight. Dyspareunia might be anticipated, but the diminution in libido with diminished secretion of the cervix, etc. are other no less important factors.

(c). Vaginal pH variations. (Chart 2, opposite).

Total number of Estimations	89	
pH under 5	16	(18%).
" over 5	73	(82%).

(Chart 3). BACTERIOLOGY.

	Radium.				Normal.	Hyst. only.	Hyst. + 1 Ovary.	Hyst. + 2 Ovaries.
	Before 40	41+	46+	51+				
Doderlein B. Pure ...	3	4	15	2	9	21	12	6
" Almost Pure .	1	6	1	4	8	5	4	5
Mixed Organisms	6	18	17	11	33	14	17	20
Occ. Cocci	-	-	-	-	11	1	-	4
Nil.	-	1	2	-	1	-	-	4

In comparison the castrate group had one or 3% with a pH of under 5, while in the normal group (on average considerably older), there were four (8%). It is again striking to contrast those cases retaining active ovarian tissue after hysterectomy, where 23 or 37% had a pH of under 5. In some cases the pH estimations, for technical reasons, may not always be reliable, but they at least correspond with the other vaginal findings, viz. Epithelium, Bacteriology, etc.

(d). Bacteriology.

Pure or almost pure Doderlein Bacilli were noted in the various groups as:-

Radium Menopause	36	(31.6%)
Normal Menopause	17	(34%)
Hysterectomy + Ovarian tissue left	42	(51.5%)
Castrates	11	(28%)

Again the highest percentage or nearest approximation to normal was found in those cases with ovarian tissue, the other groups being practically alike. (See chart 3). The presence of a pure or almost pure flora of Doderlein B. only confirms the normal state of the vagina.

(Chart 4).

VAGINAL SMEARS.

	Radium.								Normal.		Hysterectomy with Ovarian Tissue left.		Hysterectomy + 2 Ovaries removed.	
	Before 40		41+		46+		51+							
		%age.		%age.		%age.		%age.		%age.		%age.		%age.
Grade III	12	100	23	74.2	18	69.2	13	77.2	47	79.6	67	100	28	66.6
" II		-	5	16.0	5	19.2	3	16.7	8	13.6		-	7	16.7
" I		-		-	2	7.7	1	3.56	4	6.8		-	6	14.3
Combined Type		-	3	9.7	1	3.8	1	3.56		-		-	1	2.4
VAGINAL HISTOLOGY.														
Normal	9	100	30	100	20	77.0	17	73.6	15	65.2	34	93.0	18	72.0
Mod.Senile		-		-	3	11.5	5	22.1	4	17.4		-	2	8.0
Senile		-		-	1	3.8	1	4.3		-		-	3	12.0
Combined Type		-		-	1	3.8		-	4	17.4		-		-
Vaginitis		-		-	1	3.8		-		-	1	7.0	2	8.0

(e). Vaginal Smears. (See Chart 4).

Of 87 smears of the vagina 66 (83.5%) were normal or Grade III (i.e. in nine cases out of ten they were taken from normal mucosa). Of the remaining 21, 13 were Grade II, 5 were "Combined" type, and 3 were Grade I.

(f). Vaginal Mucosa.

Results: (See Chart 4).

Total No. of Biopsies	88	
Normal histology	76	(86.4%)
Senile changes	11	(12.5%)
Vaginitis	1	(1.1%)

The age factor, which was found to be of little importance in the normal menopause, appears to be of significance in the radium group; 39 cases under 45 years of age all proved to have a normal vaginal mucosa. In the "50 and under" group 20, or 77%, were normal, in the "51 and over" group 17, or 73.6%, were normal. In the course of years the cases having had the menopause induced by radium may acquire a senile type of epithelium in a higher percentage of cases. This would explain the surprising result in the normal menopausal women investigated (average age 63), when only 65.2% had normal vaginal mucosae, whereas 88% of the radium menopause group (average age 49) had normal mucosae.

The castrate group, 25 in number, had normal mucosa in 18 cases or 72%.

Of the 35 cases with ovarian tissue left in situ at the operation of hysterectomy, all had normal vaginal mucosa/except one who had definite vaginitis.

(g). Glycogen Content of Vaginal Mucosa.

The substance which is taken to be glycogen in the vaginal mucosa has certain reactions which we have tested. The iodine stain is well known, and this is used in the "Schiller Test" for carcinoma cervicis. Further, we have stained sections with Best's carmine stain with controls on which ordinary human saliva has been allowed to act. Those acted on by saliva were practically clear of red staining material, i.e. glycogen. The presence of glycogen is taken to be normal in the adult, but in children over three months and in post-menopausal women, its presence is supposed to drop to minimal amounts or to be absent (7). We have examined in all groups (including normal women, infants, women suffering from amenorrhoea, etc.) about 250 sections. The amount of glycogen present varied, but in all sections it has been shown. In the thin type of epithelium, where a diminished glycogen content would be expected great variations exist; of 16 of the senile or moderately senile types of mucosa, seven showed "moderate" glycogen staining, one "abundant"

and eight "traces". In the normal groups of epithelium variations - often dependent on the freshness of the carmine stain - were noted. It is obvious then that there can be little significance in the amount of glycogen demonstrated by staining methods. It is interesting that all epithelium showed glycogen; even in marked vaginitis where patches of the mucosa were desquamated, the healthy areas had glycogen deposited throughout the layers of epithelium. In the normal post-menopausal women the following chart shows that even in old women there may be glycogen deposited in the mucosa.

No.	Age.	Epithelium.	Glycogen.
1.	76	Normal.	Moderate.
2.	61	Mod. senile.	Trace.
3.	77	Normal.	Abundant.
4.	72	Combined type.	Trace.
5.	73	Normal.	Moderate.
6.	70	Normal.	Trace.
7.	77	Normal.	Abundant.
8.	76	Normal.	Moderate.
9.	61	Mod.senile.	Trace.

Of nine cases over 60 years of age, six had normal epithelium and in three some degree of senility. Glycogen was present in the normal epithelium in moderate amounts (3), or traces (1), or abundant (2), while the

senile epithelium showed glycogen in traces in all three cases. The fact that two cases, aged 77, had abundant glycogen in their epithelium which was of normal thickness is surprising, but is in line with the other vaginal findings reported above.

(h). Correlation of Symptoms and Signs of the Menopause.

It might be anticipated that the factor or missing factor which causes flushing of the face with sweating, etc. might be the same as that causing atrophic changes in the vagina. Salmon and Frank (57), using the vaginal smear technique, have found that no relationship existed between the type of smear and the severity of flushing. Four of their patients had very severe menopausal symptoms, but showed constantly normal smears, while four with no symptoms showed smears which suggested senile changes in the epithelium.

Our experience agrees with these findings, but we have chosen to compare the histological condition of the vaginal mucosa and the incidence of flushing. In the radium group, the following chart shows the lack of relationship between the two.

Flushing:	Nil.	Mild.	Severe or Mod.Severe.
Epithelium:			
Normal	10	34	24
Senile or Mod. Senile	2	8	5
Combined type .	0	2	0
Vaginitis	0	0	0

Of twelve cases free from symptoms, two had senile epithelium, while, of 44 with mild flushings, ten had some degree of senility of epithelium. Twenty-nine cases had moderately severe or severe flushings, but only five had senile changes of the epithelium. It may be said, then, that in this series of patients with the menopause induced by radium, no close relationship exists between the incidence or severity of flushing and the type of vaginal mucosa. It may be that the factor which causes flushing may be a different one to that causing genital changes, and some facts are available from the literature. It is believed by some (62, 63 et al) that A.P.H. is in excessive amounts in the circulation in the menopause and this results in vasomotor disturbances, of which flushing is an example. Fluhman (63) tried to find some connection between the excretion of A.P.H. in the urine and the type of vaginal smear, but no correlation was proved, and he concluded

that there must be one factor related to or causing flushing, in his belief A.P.H., while another factor is responsible for changes in the genital tract.

The problem is still sub judice and is obviously not simple.

Summary of Changes following Radium Therapy.

1. Flushing occurred in 41 or 47% of cases before the menopause was induced, but in no case under 40.

2. Flushing of severe or moderately severe type was recorded in 39 or 43.6% of cases following radium therapy, and this figure compares roughly with the castrated cases (47%).

3. Three cases who had a spontaneous menopause followed by persistent flushing were apparently cured by radium therapy, while in two there was no improvement.

4. Genital changes following radium: (a). 16 or 24% had atrophic labia minora.

(b). "Stenosis of the vagina" occurred in 61 cases (67%) against 33 or 77% of the normal menopausal cases (whose age is greater on average).

(c). pH estimations were carried out in 89 cases, 16 (18%) were called "normal" (under 5).

(d). A pure or almost pure flora of Doderlein B. occurred in 36 cases (31.6%).

(e). 66 or 83.5% of vaginal smears were of normal Grade III type.

(f). 88 vaginal biopsies were studied. 76 (86.4%) were normal, 11 (12.5%) had senile changes, one (1.1%) had vaginitis.

(g). Glycogen has been found in variable amounts in every section stained so far (250 in all). Little significance can be deduced from its presence, quantitatively assessed by staining methods.

5. Correlation of Flushing and Vaginal Histology was not possible; of twelve cases free from flushing, two had senile epithelium, while, of 44 with mild flushing, ten had senile changes of the mucosa; of 29 cases with severe or moderately severe flushing, only five had senile changes of the vaginal mucosa.

DISCUSSION of the FINDINGS of the RADIUM MENOPAUSE.

A. Therapeutic Results:

The results, with three exceptions, in this series were successful. The simplicity of technique, the low morbidity rate and the absent mortality rate in this series (and in most of those quoted in the literature) commend the use of radium.

B. After Effects:

Contrary to Hunter's view (50), the after-effects appear to be fairly severe in a certain proportion of cases. In the present-day use of Stilboestrol and other

oestrin preparations to control symptoms, we may have an agent which offsets these disadvantages. It must be remembered in this connection that hormone treatment is still expensive; it may have to be prolonged over months and, further, cessation of treatment is frequently followed by alarming oestrin-withdrawal uterine haemorrhage.

Changes in the external genitalia are negligible, but atrophic changes in the vagina are common, although probably rarely causing symptoms. The mucosa is healthy in a high proportion of cases, and only one case of definite vaginitis was found, although in eleven cases the mucosa was thinned and might conceivably become infected at a later date.

C. Hormone Action:

The presence of some oestrin-like hormone can be presumed from the evidence both subjective and objective. The vagina has been described before as a roughly accurate mirror of ovarian function. There were, in this series, a high proportion of cases with vaginae akin to a normal sexually adult woman, i.e. the vagina appeared normal, smears, bacteriology and histology were normal. Several women have had their urinary output of oestrin estimated and the results will follow in another paper; they tend to support these views.

D. The Efficacy of Vaginal Smears in assessing Oestrin Therapy.

Many clinics use the fact that oestrin will produce a completely normal type of vaginal smear, to gauge the efficacy of their treatment (54, 57, et alii), and it has been suggested that the optimum level of oestrin may be maintained by the readings obtained from these smears. The following reasons are given for our doubting the value of this method of control:

1. There is no relationship between the type of smear and the severity of the symptoms (57), and we have shown there is none between the type of histology and the severity of symptoms.

2. The mucosa may be normal at the outset of treatment, i.e. it may not be capable of showing marked changes under oestrin therapy. In 29 cases who had flushings of severe or moderately severe type, only five had senile mucosae, the remainder being normal. So that 24 cases having normal mucosa would not be capable of showing marked changes, unless, possibly a little thickening, following oestrin therapy.

3. We have found in one case that oestrin in small doses could relieve the patient's symptoms without altering to a notable extent the state of the vagina.*

For these reasons it is suggested that the present use of vaginal smears as an index of the success of oestrin therapy is only of practical value in a small percentage of cases.

---

* Mrs. T. now 46 years. Radium menopause 24.1.37. Had severe flushings which compelled her to consult her doctor who injected oestrin (doubtful dosage) at weekly intervals for the three months previous to her reporting to this clinic. Her flushing had practically disappeared under oestrin treatment.
Vaginal Smear: pH 6.1.
Cells mostly deeper stratum spinosum in type with a good proportion of large squames and pus. Classified "Combined type".
Histology: 2-layered type averaging 210, i.e. lower limit of normal.

Chapter 6.

SURGICAL INDUCTION OF THE MENOPAUSE.

The advantages and disadvantages of radium in its simplicity, efficacy and safety have been stated. There are still cases where hysterectomy is to be performed, even with its attendant mortality of about 2% or more. Martindale quotes the figures of Polak (U.S.A.) and Gauss (Germany), which were reported before 1933 (69). The former treated 906 cases and chose operation in 77%, while the latter operated on 15% of 1048 cases. These figures present in striking fashion the different views which are at present held in various clinics throughout the world in regard to the treatment of uterine haemorrhage.

Material:

Hysterectomy	39
Hysterectomy + Unilateral Salpingo-oophorectomy	34
Hysterectomy + Bilateral Salpingo-oophorectomy	43
Bilateral oophorectomy only ..	2
Total.-	118

The two cases of bilateral oophorectomy are included in the castrate group totalling 45; also one case had hysterectomy with bilateral oophorectomy after the onset of the menopause.

The method of investigation was similar to that of the normal and radium groups. Following a study of the patients who had hysterectomy with retained ovarian tissue, it was found that no difference existed between them as groups, i.e. one ovary appeared to be as satisfactory as two in its action, after removal of the uterus, so that the two have been grouped together for comparison with the castrated group. The duration of the menopause in the surgical group was, in the majority of cases, two years, the shortest being three months. In the radium menopause it appears that if symptoms are going to occur they do so immediately after treatment. After hysterectomy however, this is not always true.

For example, Case 689. Present age 45. On 13.10.37 she had subtotal hysterectomy performed. No flushing or other menopausal symptoms followed, but two years later she developed moderately severe flushing with sweating and occasional headache. These symptoms persisted for the six months previous to her examination at this clinic.

If the series of cases which had hysterectomy performed with conservation of ovarian tissue were to be investigated after eight or ten years, it is feasible that a proportion of them would have had symptoms of the menopause commencing at a time when the menopause would

(Chart 1). INCIDENCE OF FLUSHING.

	Before 40		41+		46+		51+		Normal.		Hyst. only.		Hyst. + 1 Ovary.		Hyst. + 2 Ovaries.	
A. Before the Menopause.		%age		%age		%age		%age		%age		%age		%age		%age
Nil		-	21	65.6	16	41.0	11	61.0	37	50.0	31	88.6	23	69.7	31	75.6
Present		-	11	34.4	23	59.0	7	39.0	37	50.0	4	11.4	10	30.3	10	24.3
Doubtful		-		-		-		-	10	-		-		-	4	-
B. After the Menopause.																
Nil		-	4	12.89		-	1	5.9	24	30.7	13	36.1	19	57.6	5	11.6
Mild	5	50.0	16	51.61	20	55.0	10	59.0	41	52.5	21	58.3	14	42.3	18	41.9
Mod.Severe	4	40.0	9	29.03	7	19.4	4	23.5	10	12.8	*1	2.8		-	11	25.6
Severe	1	10.0	2	6.45	9	25.0	2	11.7	3	4.0	+1	2.8		-	9	20.9
Doubtful		-		-		-		-	6	-		-		-	2	-

* Flushings followed two years after operation.

+ Severe flushings followed hysterectomy at 56 years of age.

have occurred spontaneously, had no operation been performed. In other words, freedom from symptoms after operation may in some cases be merely their postponement.

SYNOPSIS OF RESULTS (Chart 1).

A. Flushing.

Only 24 cases had flushing before operation. This is to be expected, since at the time of operation the patients had rarely reached the age at which climacteric symptoms commence.

Flushing after Hysterectomy.

	Hyst. only.		Hyst. + 1 ovary.		Hyst. + 2 ovaries.	
None	13	36.1%	19	57.6%	5	11.6%
Mild	21	58.3%	14	42.3%	18	41.9%
Mod.Severe .	1	2.8%		-	11	25.6%
Severe	1	2.8%		-	9	20.9%
Doubtful ...		-		-	4	-

With retention of ovarian tissue only two (3%) were seriously upset by flushing. These cases were:-

No. 689. Moderately severe flushing, commenced two years after operation, following which there had been no flushing.

No. 2285. Aged 56, had severe flushing and sweating attacks after removal of the uterus.

In contrast removal of both ovaries was followed by flushing in 20 cases (47%), moderately severe in eleven and severe in nine. The advantage of retaining ovarian tissue at the operation of hysterectomy is apparent, with a view to preventing menopausal symptoms. Hendry (70), however, writes: "In the past nine years I have operated on 33 patients for removal of ovaries conserved at previous operation - in 29 there had been simple cyst formation; in two ovarian sarcomata and in two granulosa cell tumours", so that this authority, although in favour of retention of ovarian tissue when possible, strikes a warning note against the practice of always retaining part or all of the ovarian tissue at the operation of hysterectomy. Nevertheless, the incidence of 33 cases of post-operative cyst formation over a period of nine years, although apparently a large number would require to be controlled with a large series of normal women who might develop cysts, before the conclusion can be reached that the ovaries or parts of ovaries left in situ at operations in the pelvis will form cysts in a higher percentage of cases than normal. Both in the control of flushing and (as will be shown) the preservation of a healthy vagina, ovarian tissue is essential.

B. Genital Changes following Hysterectomy.

The changes in the external genitalia in 106 cases

examined were negligible; only four out of 35 castrated cases showed some atrophy of the labia minora. Clinical examination of the mucosa of the vagina was normal in all cases with ovarian tissue, but in the castrate group definite changes in the mucosa were obvious in 16 out of 36 cases (44%); details of these changes visible to the naked eye in the castrated group are as follows:-

Normal mucosa	20	56%
Red appearance & smooth	8	44%
Smooth + punctate red spots (resembling vaginitis)	4	
Pale and smooth	4	

Further detailed vaginal investigations in this group are given in synopsis (i.e. in cases of surgical menopause).

(a). pH Estimations.

The results show further confirmatory evidence in support of conservation of ovarian tissue, and comparative figures are available, (Chart 2).

pH 5 or less:

Hysterectomy + Ovarian tissue left.	23	37%
" No Ovarian tissue left.	1	3%
Radium Menopause	18	19%

(b). Bacteriology.

Again confirmatory evidence is obtained in favour of retention of ovarian tissue:-

Pure or Almost Pure Doderlein Bacilli.

Hyst. + Ovarian tissue left	42	52%
" No " " "	11	28%
Radium Menopause	36	32%
Normal Menopause	17	34%

(c). Vaginal Smears.

	Grade III.		Grade II.		Grade I.		Combined Type.
Hyst. + Ovarian tissue left	67	100%		-		-	-
Hyst. + Both Ovaries out	28	66.6%	7	16.6%	6	14.3%	1 2.4%

(d). Vaginal Epithelium.

Epithelium:	Normal.		Mod. Senile.		Senile.		Vaginitis.
Hyst. + 2 Ovaries left	20	100%		-		-	-
Hyst. + 1 Ovary left.	14	93%		-		-	1 7%
Hyst. + 2 Ovaries out	18	72%	2	8%	3	12%	2 8%

The lack of ovarian tissue leads to senile changes in the vaginal mucosa in 20% of cases (or 28% if Vaginitis is included), which is higher than the figure obtained from the study of 98 biopsies from patients who had the menopause induced by radium, when senile changes occurred in 12.5% (or 13.6% if vaginitis is included).

Do castrated women commonly suffer from Vaginitis? The question is difficult to answer, since other factors than the health of the vagina must be considered, such as

Chart 5. CHART SHOWING THE VALUE OF OVARIAN TISSUE.

	Ovarian Tissue.		Castrates.	
Flushings: Severe, Mod.Severe)	2	3%	20	46.5%
Vaginal pH 5 or less	23	37%	1	3%
Pure or almost pure Doderlein B.	42	52%	11	28%
Grade III Smear	67	100%	28	66.6%
Grade II, I, Combined	0.	0%	14	33.3%
Normal Histology	34	97%	18	72%
Senile Histology	1	3%	7	28%

the diminished frequency of coitus in the menopause. However, it would appear that in a higher proportion of cases, vaginitis of post-menopausal type is more likely to occur.in castrated women than in those with ovarian tissue. In two cases vaginitis was proved histologically, and the figure is high for such a small series (25 biopsies). The matter is discussed more fully under "Vaginitis" (Chapter 7).

CONCLUSIONS. (See Chart 5 opposite).

1. The conservation of ovarian tissue is almost certain to prevent menopausal flushing after the operation of hysterectomy.

2. Apart from the effect of surgical closure of the upper vagina little change occurs in the genitalia following the operation of hysterectomy.

3. Castration caused flushing in 78% of cases, severe or moderately severe in 47%.

4. Castration is followed by senile changes in the vagina, e.g. the mucosa shows senile changes in 28% of cases, compared to 13.6% after the radium menupause.

Chapter 7.

THE DIAGNOSIS OF VAGINITIS.

It follows naturally from this study of the vaginal mucosa that some remarks on the question of the diagnosis of vaginitis should follow, especially since a proportion of post-menopausal women develop this condition.

Davis (59) reported that 330 out of 1000 consecutive cases reporting to his clinic had to wear a pad for leucorrhoea. Not all of these cases had vaginitis, so that a rough clinical definition is necessary for the wider term 'leucorrhoea'. Sharman and Cruickshank (15) suggest that leucorrhoea is "that degree of discharge (other than blood-stained) sufficient to soil the clothes or to necessitate the use of a sanitary napkin and considered by the patient to be an appreciable departure from normal." It is a well-known fact that the sensibility of the individual patient to discharge varies greatly. A complaint of discharge may be the first symptom to bring the patient under observation. Yet it must be recognised that the condition occasionally exists without complaint. In two cases examined by us, abundant pus with trichomonas led us to take biopsy specimens, although

they had no symptoms. Confirmation of vaginitis was obtained histologically in both these cases.

Secondly, the clinical appearance of the vulva is noted. This may be covered with purulent discharge and even show a degree of vulvitis perhaps resulting from the vaginal discharge. The appearance of the vagina varies and may be normal or spotted with red areas. Simply by looking at the vagina of a sexually mature woman it may be clinically sound to diagnose vaginitis on its appearance, but in senile or post-menopausal women it is not so easy. Significant facts have been collected in this study to emphasise that further knowledge is needed of the variations from normal which may exist in the vagina of post-menopausal women, before a clinical diagnosis can be made simply by observations made on the vaginal wall. 58 cases of normal post-menopausal women were examined by speculum. In 29 (58%) the vagina did not appear normal. In 14 the mucosa was pale and smooth. In 15 it was smooth and studded with red areas exactly as "true" vaginitis after gently swabbing the vagina. 11 of these mucosae were examined histologically; in no case of the "red spotted group" was there histological evidence of vaginitis, so that a clinical diagnosis of vaginitis was not supported. In two out of six cases with "pale, smooth" mucosa there was thinning to 130 u and 165 u, respectively,

i.e. moderate senility; the other four cases being normal. So that simply by looking at the mucosa in a post-menopausal woman who may complain of some discharge it is impossible, without a biopsy, to state definitely if she has vaginitis.

Thirdly, the examination of vaginal contents by wet-drop and bacteriological and chemical methods is necessary in the diagnosis. The presence or absence of pus in the vagina appears to be of little significance and varies from patient to patient. In this group of post-menopausal women it was almost invariably present. The types of cell from the surface epithelium is a poor index of the condition, thickness and health of the underlying mucosa (vide supra) unless this approximates to normal (Grade III) when nine times out of ten the underlying epithelium will prove to be normal.

The wet-drop examination for trichomonas has been carried out in 260 cases and in fourteen the organism was found. None of these patients had abnormal amounts of discharge, but two out of nine cases examined histologically showed the typical picture of vaginitis. Seven cases were free from symptoms and pathological evidence of vaginitis. So that merely to find pus and Trichomonas on a wet drop suspension is not sufficient evidence for a diagnosis

of vaginitis. Mohr (66) found trichomonas in 52.6% of 212 women examined, in none of these was there evidence of vaginitis. Mohr therefore doubts if the term "Trichomonas Vaginitis" is justifiable, since his investigations lead him to doubt the specificity of the trichomonas as the causal organism, and our investigation tends to support this view.

The type of organism present in the normal woman is predominantly B. Doderlein. As stated above, wide variations are found in patients, especially after the menopause, when B. coli, etc. abound. So that there is little value in the stained vaginal smear in a case complaining of leucorrhoea unless pure Doderlein B. (or almost pure) are obtained, when the discharge is invariably normal, i.e. it contains little except large flat squames. If this normal discharge is found, the "leucorrhoea" can be taken as an excessive outpouring of normal vaginal secretion and excessive amounts of cervical mucus should be tested for by examination of a tampon left in the vagina for twelve hours.

pH studies are similarly of little value unless they prove to be under 5, when, practically always, a normal smear and histological picture will be obtained. The presence of an alkaline pH signifies little in post-menopausal women since the majority of them are normally alkaline.

The result of vaginal biopsy to confirm the diagnosis might appear an absolute finding. The following microphotographs (20, 22) show a well developed "senile" vaginitis in a post-menopausal woman aged 48.

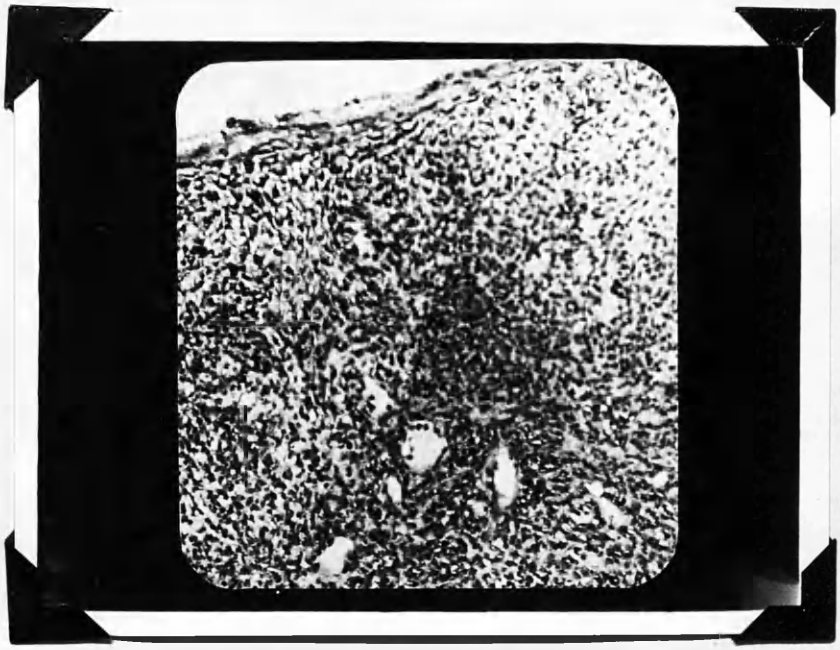

Fig. 20. Acute Post-menopausal Vaginitis.

Mrs. D. aged 48. Radium menopause at 46. Intense infiltration of lamina proprium with round-cells; dilatation of blood vessels; almost complete desquamation of this area of epithelium.

Best's stain X 146.

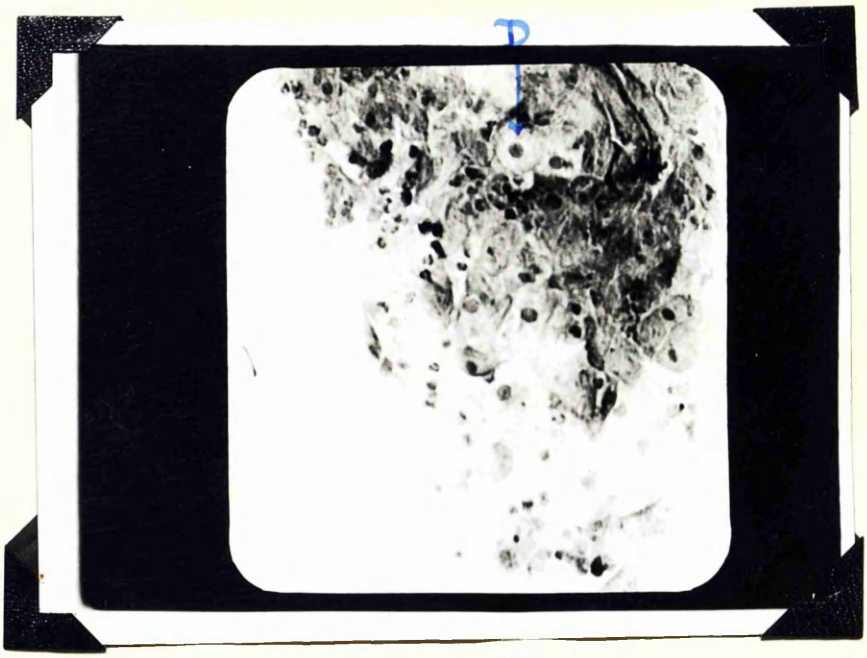

Fig. 21. Vaginal Smear in Vaginitis.

Vaginal smear from the case above (Fig. 20).
Mixture of pus cells and deep epithelial cells (D).

Papinicolau's Stain X 224.

There is superficial desquamation of epithelium, marked inflammation of the lamina proprium and diminution in glycogen content of the epithelium. The desquamation may affect the mucosa in a patchy fashion, the intervening areas appearing quite normal. This picture is in contrast to that obtained after treatment with small doses of Stilboestrol, Figs. 22 and 23.

Fig. 22. Vaginitis cured by Stilboestrol.

Mrs. D. (case above) after 28 mgm. of Stilboestrol. 3-layered normal epithelium. Lamina proprium free from round cells. Best's Stain X 60.

Fig. 23. Vaginal Smear after Stilboestrol.

Grade III Smear (flat squames only). In this case a reliable gauge was obtained from the smear of the actual condition of the mucosa (see Fig. 22).

Papinicolau's Stain X 224.

The presence of round cells perhaps in small clumps in the lamina proprium is mentioned by Bloom and others as being normal. Smith & Brunner (18) state that there may be five grades of infiltration, the first three being within "physiological limits". Our own findings with regard to round cell infiltration of the sub-epithelial tissue is that it is a relatively rare occurrence, if one neglects a few scattered cells throughout the lamina proprium. Definite infiltration of diffuse or in focal type occurred only seven times (4.9%) in 142 cases in which the menopause had been induced. The chart below shows the findings in each case and, where possible, microphotographs are presented:

Round-Cell Infiltration of Lamina Proprium.

No.	Type of Menopause.	Discharge.	Epithelium (Thickness).	Round Cell Infiltration.	Vaginal Mucosa per Speculum.
327	Hysterectomy + 1 ovary (Fig. 24). p.91.	None.	Normal 192 u	+	Doubtful.
866	Hysterectomy + 2 ovaries (Figs.26 & 27) p.96 & 97.	None.	Senile 90 u.	+	Pale: smooth.
2259	do.	?	Mod.Senile: 156 u.	+	Normal: Tends to peel.
1598	do. (Fig. 25). p.92.	Yellow ++	Normal 420 u.	++	Red ++. Bled with ease.
952	do. (Figs.28, 29). p. 98 & 99.	None.	Mod.Senile: 167 u.	+	Normal.
85	Ra. Menop. (Figs.30, 31). p.100 & 101.	None.	Senile: 89 u.	+	Normal.
48	Ra. Menop.	None.	Mod.Senile: 115 u.	+	Pale: Smooth.

In case 327 the patient had one ovary retained at the operation of hysterectomy two years ago. She had no leucorrhoea and being a virgin only the tip of the speculum could be inserted to permit taking a biopsy, so that no full report is available on the appearance of the mucosa. The pH of the discharge was 5.2 and the smear normal, Grade III. Trichomonas were detected. Histologically the epithelium appeared normal, except for areas with lymphocytic foci (fig. 24).

Fig. 24.

Miss A. Virgo. aged 42. Hysterectomy + 1 ovary removed 2 years ago.

Normal 3-layered epithelium 196 u thick. Subepithelial round-cells (R).

Best's Stain X 215.

This case could therefore not be diagnosed as vaginitis, since she had neither leucorrhoea nor histological vaginitis.

In case 1598 the patient complained of leucorrhoea and there was a large quantity of pus in the vagina containing many trichomonas. The vagina was red in patches and a diagnosis of vaginitis was made. Despite this the length of vaginal mucosa examined (about $\frac{3}{8}$") showed only one small round-cell focus and no desquamation (Fig. 25).

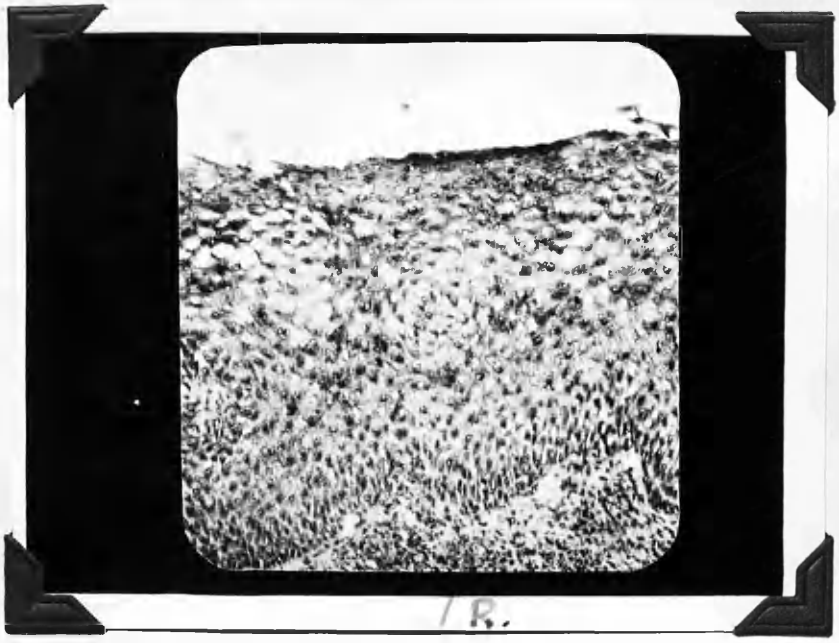

Fig. 25. "Clinical" Vaginitis.

Mrs. M. (1598), aged 47. Uterus and 2 ovaries removed 5 months ago.

Epithelium appears normal except for Round cells (R.) in Lamina proprium. Thickness: 420 u: Best's Stain X 136.

In only one out of seven cases (viz. 1598) was a diagnosis of vaginitis justified on clinical grounds. The remainder did not complain of leucorrhoea, yet on speculum examination they showed obvious variation from the normal in three cases (see Chart p. 90), two being apparently normal, one being doubtful. The epithelium was senile more or less in five cases and normal in one.

These six cases are insufficient to draw conclusions from, but it would appear that they possess a type of epithelium, thinned considerably and showing

abnormal numbers of lymphocytes and plasma cells in the sub-epithelial tissue.

It is of interest that 32 cases out of 34 who had hysterectomy performed with conservation of ovarian tissue had normal vaginal epithelium and showed no evidence of thinning or round cell infiltration of the sub-mucosa. The two exceptions were one case of vaginitis and case 327 mentioned above. It would appear therefore, that active ovarian tissue will usually prevent the formation of the type of epithelium mentioned in the above six cases.

Support for this hypothesis is given by the appearances of the mucosa of a child before the menarche when the ovaries are not active. The lining epithelium is then undifferentiated and there is round cell infiltration of the submucosa, in fact, a histological picture similar to a desquamated patch of mucosa in adult vaginitis in which, however, normal areas are usually seen alternating with the denuded areas. (Fig. 32).

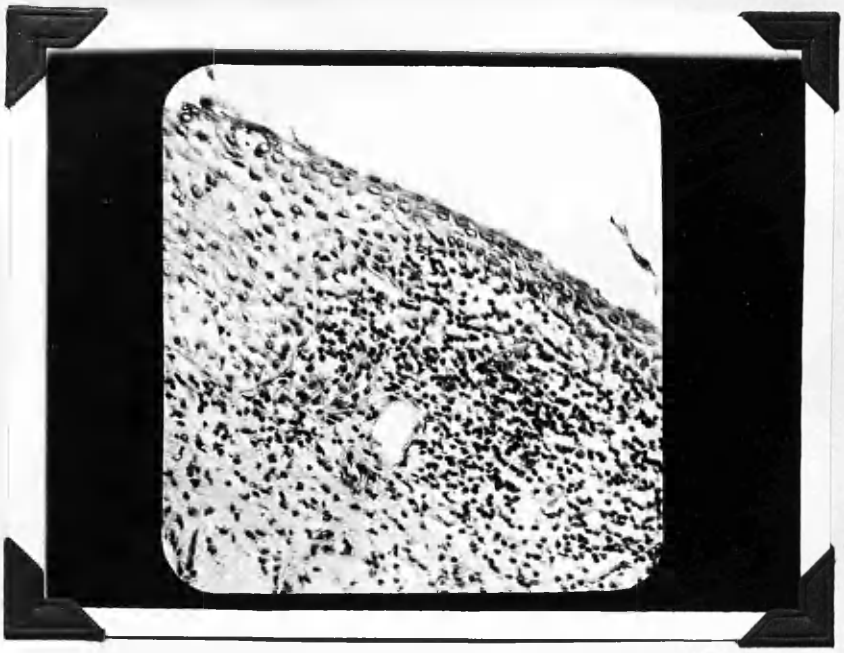

Fig. 32. "Pre-Vaginitis" in a child.

Miss M. Normal case, aged 12.

Vaginal mucosa lined by two layers of small cells. Round cells infiltrate the submucosa. Note similarity to Fig. 31. Best's X 94.

It is suggested therefore, that in some post-menopausal women there may develop a thin type of vaginal epithelium - a "pre-vaginitis" - which may be specially liable to infection.

No attempt can be made here to discuss the problem of vaginitis in the sexually mature woman. Some women are infected, some are not. Oestrin has no effect on mucosa under normal ovarian control, and in no way alters the course of vaginitis if given therapeutically in the sexually mature woman, so that

it seems likely that predisposing factors other than oestrin-deficiency exist in the normal adult woman to determine which cases are infected, e.g. masturbation, sexual intercourse or disturbed sugar metabolism, etc. But the problem probably merges into one of general mucosal infections of the nose, throat and ears, and is truly a vast one.

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CONCLUSION.

The diagnosis of Vaginitis in post-menopausal women especially, is not easy. The fallacy of relying solely on one line of investigation is pointed out. It appears that correlation of clinical findings with histological examination of the vaginal mucosa offers the most definite basis for diagnosis. It is suggested that in the histological diagnosis of vaginitis a sound knowledge of the variations met with in the normal post-menopausal mucosa is essential.

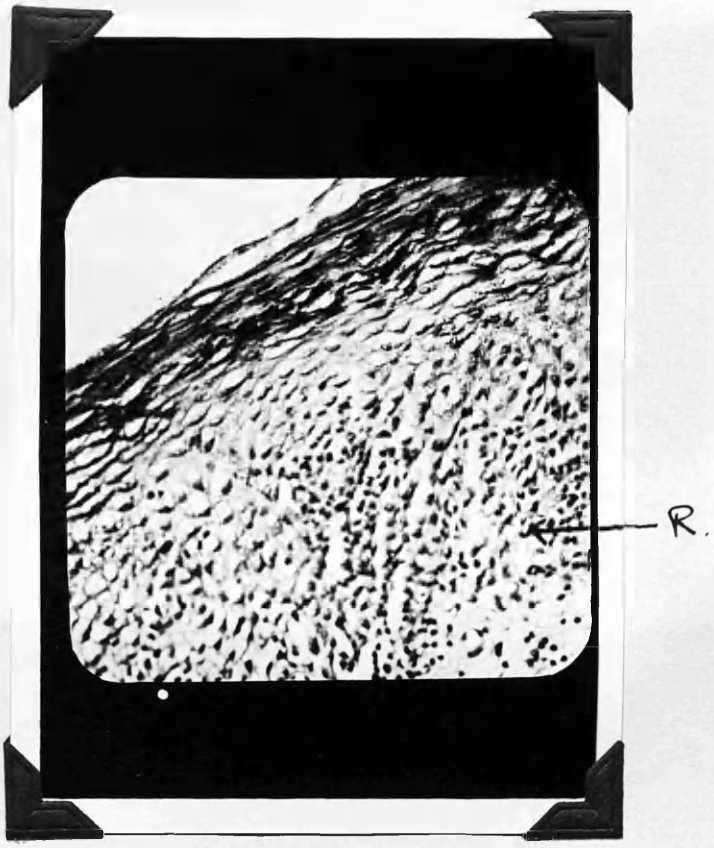


Fig. 26. "Pre-Vaginitis".

Mrs. G. (866), aged 52. Uterus + 2 ovaries removed 18 months ago.

Epithelium senile, 90 u. thick. Note Round cells (R) infiltrating the stratum spinosum.

Best's stain X 215.

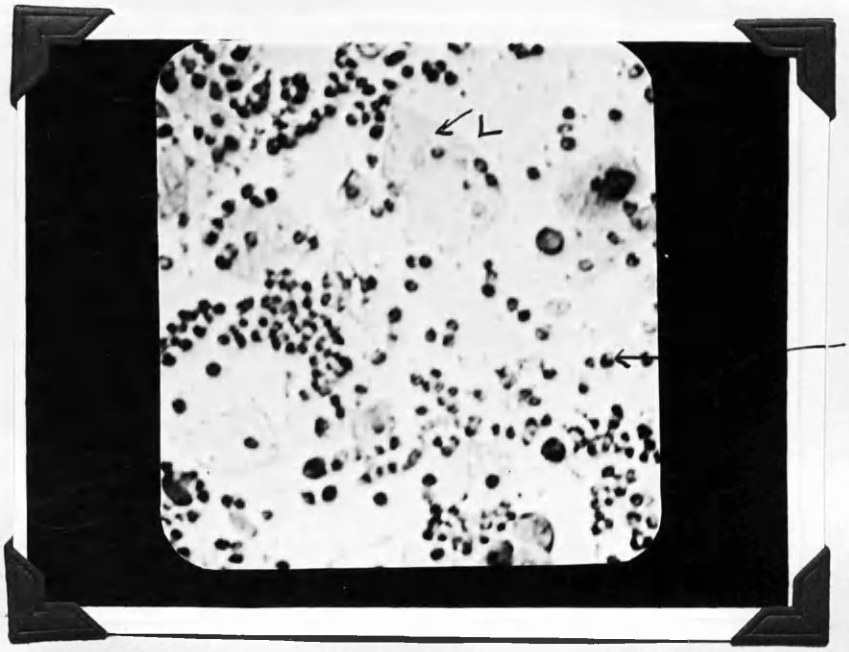


Fig. 27.

Mrs. G. (866). Vaginal smear (from above case, Fig. 26), showing large squames (L) and leucocytes. (W.B.C.)

According to our classification Grade III, i.e. "normal" smear, which is not in accord with the epithelium, fig. 26.

Papinicolau Stain X 215.

Fig. 28. "Pre-Vaginitis".

Mrs. M. (952), aged 46. Uterus and 2 ovaries removed 2 years ago.

Epithelium 167 u. thick, somewhat desquamated. Marked round cell infiltration of submucosa marked.

Best's Stain X 136.

Fig. 29.

Miss M. (952).

Vaginal smear from above case (fig. 28). Flat squames and only occasional leucocyte, classified Grade III; this is at variance with the epithelium, fig. 28.

Gram Stain X 215.

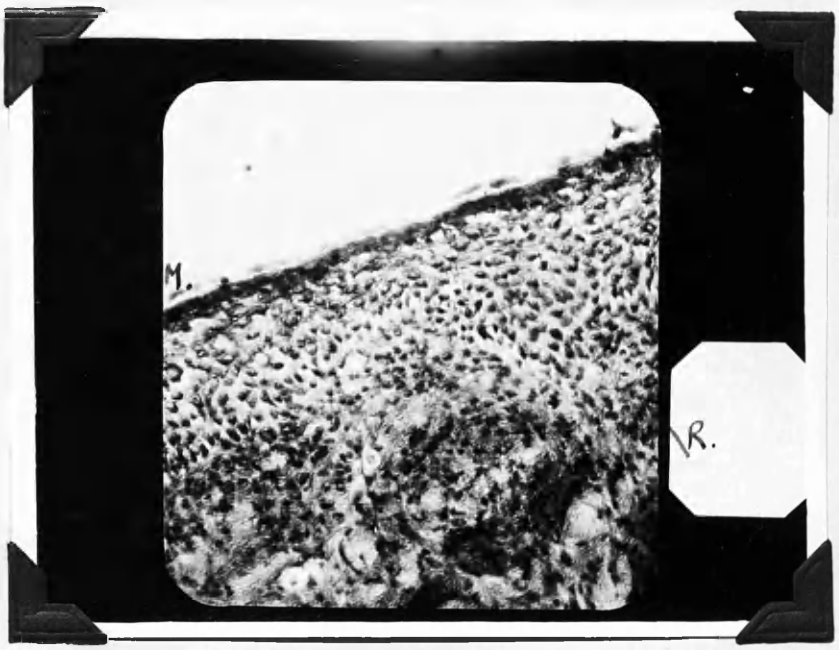
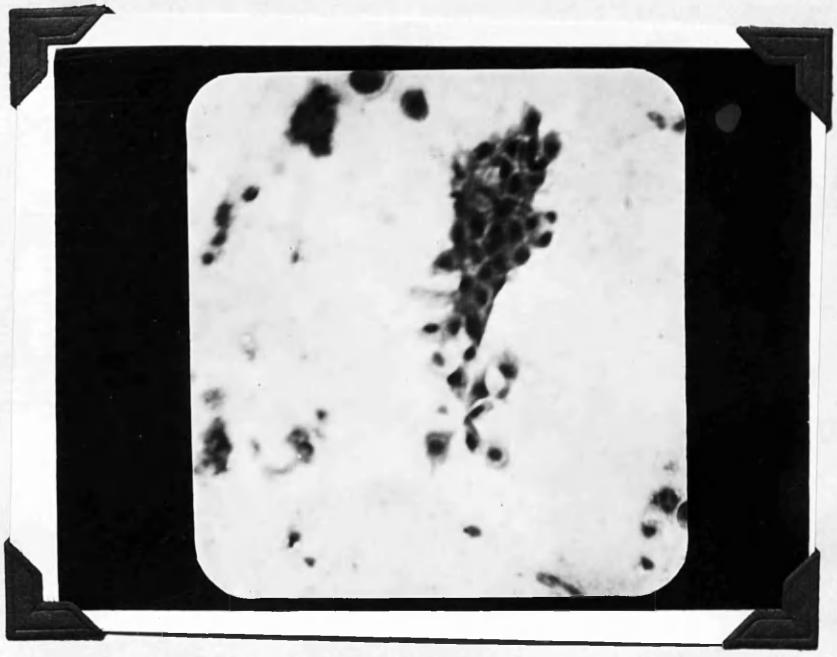


Fig. 30. "Pre-Vaginitis".

Mrs. C. (85), aged 47. Radium Menopause at 45.

Senile Mucosa (M) with round-cell infiltration of submucosa (R).

Best's Stain X 215.



Case No. 85. The smear produced small cells with relatively large nuclei, which corresponds to the type of epithelium shown in fig. 30. The cells are deep stratum spinosum cells, little removed in development from the basal stratum germinativum cells.

Papinicolau's Stain X 215.

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