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Metropathia haemorrhagica

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METROPATHIA HAEMORRHAGICA

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METROPATHIA HAEMORRHAGICA

In the child bearing period of life healthy women menstruate at regular intervals and apart from pregnancy and lactation it is the rule, with normal women, that this cycle is maintained from puberty until the menopause. The majority of gynaecological patients seek medical advice for irregular vaginal haemorrhage and in many cases the cause of this abnormal haemorrhage is assigned to such pathological conditions as carcinoma of the cervix, carcinoma of the body of the uterus, uterine myomata, and uterine polypi, which can be demonstrated both clinically and anatomically. In a large number of cases although menstrual disturbances and abnormal uterine haemorrhage dominate the symptoms, gross physical abnormalities cannot be found and no satisfactory anatomical cause for the irregular haemorrhage can be discovered.

These cases are frequently labelled with such terms as epimenorrhoea, menostaxis, and metrorrhagia, which, although indicating the type of the irregular haemorrhage, offer no explanation of the cause of the abnormalities; or the cases are referred to as those of endometritis or of chronic metritis, although there is no direct evidence to show that true inflammatory lesions exist in the uterus. In such cases the pathology is adduced by a process of exclusion and in almost all, no definite evidence is brought forward to show that inflammatory reactions, comparable to those found elsewhere in the body, exist in the endometrium or myometrium.
At the present day the fallacy of this method of reasoning is generally recognized, but as the cases are common and have been known for many years under these names, very little effort has been made to investigate their pathology.

Our etiological survey has shown the need for discarding the older view which sought to explain excessive and irregular dysfunctional bleeding on the basis of purely uterine pathology. It is true that there remains an ill deemed group in which the infection of the endometrium plays a direct part but it would seem in such that the bleeding is of short duration and is prone to spontaneous cure, for these cases constitute a strikingly small proportion of the more severe cases which enter hospital for treatment and which comprise the basis of investigative material.

At the same time while there is clear evidence on which to erect a new etiology based upon a reciprocal interplay between ovary and uterus there is not yet a sufficiently sound foundation to justify more than tentative views.

Cases of irregular and excessive uterine haemorrhage are divided into two main classes (1) those in which the uterus is the seat of tumors (Fibromyoma, Mucous Polypi and Malignant Disease) or retained fragments of Placenta. (2) Thos in which such a gross uterine pathology is absent and where instead there is nothing more than changes in the endometrium, usually of a proliferative nature, with commonly, in addition, some general and uniform overgrowth of the fibromuscular wall of the uterus.

Schroeder, Beckwith, Whitehouse, Young and others directed attention to evidence suggesting that many such cases owe their
origin to disturbed ovarian function some 20 years ago. It was Schroeder who from the chaos of clinical and pathological data first succeeded in building up a condition with some semblence to a separate entity which he has termed "Metropathia Haemorrhagica" its main symptom is metrorrhagia or irregular continued bleeding and tho occurring at any age from (Puberty) menarche, onwards it is found characteristically between 40 and 50 and this term to take the place of such poorly descriptive nomenclature as chronic metritis, fibrosis uteri, myopathia haemorrhagica etc.

The earliest investigations on the pathological conditions of the endometrium followed the introduction of the curette into Gynaecology by Recamier, for with the help of the curette "fungous and granulation-like pieces of endometrium" were removed, and although the specimens on histological examination frequently showed little, if any, departure from the normal, because it was the fashion for there to be an "inflammation system" in gynaecology at the time, the conclusion was reached that the fungous condition of the endometrium was the result of an inflammation. At a later date, Rokitansky, as the result of a study of polypi of the endometrium of the body of the uterus, concluded that such polypi were found in inflammatory conditions. Further, both Rokitansky and at a later date Scanzoni maintained that acute inflammations of the uterus became chronic and gave rise to an endometrium which was atrophied and scarred with fibrous tissue. In 1875, Olshousens, under the term Endometritis Fungosa, described with considerable accuracy the characters of the endometrium in the
condition first observed by Recamier and at a later date the same condition was described by various authors under such terms as benign sarcoma, adenoma diffusum, and endometritis villosa. Matthews Duncan gives a remarkable good account of endometritis in "Diseases of Women" 1879., for he clearly emphasizes the true infective nature of most of the cases.

In 1879, Ruge, as a result of an investigation into the micro-anatomical features of specimens of the endometrium removed by curettage of the uterus, classified what he considered to be abnormal forms into three main groups of "endometritis"

(a) The interstitial form in which the stroma was infiltrated with round cells and leucocytes.

(b) The glandular form in which the main alteration was seen in the glands, which were described as swollen and tortuous. The glandular endometritis group was further subdivided into the hypertrophic and the hyperplastic types.

(c) The third group, termed the mixed form, comprised those cases in which changes of groups (a) and (b) were found together.

For a long time the classification was accepted and if a specimen was obtained which belonged to one of the groups he had indicated, the patient was diagnosed as suffering from endometritis. The first opposition to the Ruge teaching resulted from the bacteriological examination of the endometrium in these cases, for it soon became evident that bacteria could not be demonstrated in all cases labelled endometritis either by culture from the cavity of the uterus or by histological examination of the endometrium. In 1882 Brennecke suggested that the hyperplastic endometritis type
of Ruge was not the result of an inflammation but was a true hyperplasia and went so far as to state that the changes in the endometrium were the result of ovarian abnormalities. In 1891 Schmal stated that diffuse hyperplasia of the endometrium was not the result of an inflammation and insisted that this condition should be strictly separated from cases of purulent endometritis. Alto such views were clearly opposed to those Ruge little attention was paid to them, for it was undoubtedly true that Ruge's group could be demonstrated histologically and if no explanation of the glandular endometritis form was at hand other than that it represented the result of an inflammation, this view was certain to hold the field.

It is interesting to note that the origin of the modern interpretation depends upon the observation of Hirschmann, that the shape of the glands of the endometrium during menstruation closely resemble those of Opitz-Seitz in early pregnancy, and accurately correspond to the forms met with in Ruge's endometritis glandularis hypertrophica.

Hirschmann and Adler joined forces and together produced the two publications on "Endometritis" in 1907 and on "The Cyclical Changes of the Endometrium" in 1908 which revolutionized the whole conception of endometritis and perhaps more important still, diverted the attention of gynaecologists towards the fundamental physiological problems of the female generative organs.

The classical work of Hirschmann and Adler merits the highest praise. Its success was determined by the scientific method in which the investigations were made. For the first time the structure of the endometrium at various phases of the
menstrual cycle was described and with this as standard the variations from the normal could be recognized and their real significance appreciated. Perhaps the importance of the work is best realized by those whose duty it is to examine and report upon specimens of curettings. Without a knowledge of the work of Hirschmann and Adler, a true interpretation of the appearances is impossible.

The original publications of Hirschmann and Adler resulted in the publication of a large amount of work on the histology of the endometrium and although at first there was some opposition to their views, their principles have gradually become accepted. The publications of Schroeder on the changes in the endometrium during the menstrual cycle, on the whole, show complete agreement, with the exception that Schroeder indicated that during menstruation the whole of what he refers to as the functional portion of the endometrium, that is to say, the superficial and middle zones of the premenstrual endometrium, disintegrate and are shed. Schroeder also confirmed the work on endometritis, elaborated the descriptions and correlated the menstrual disturbances with the changes found in the endometrium. The histological features of the endometrium during the menstrual cycle have been given in the English tongue by Novak and by others.

The historical account that has been given above is intended to indicate the state of our knowledge at the present time of the appearances of the normal endometrium and of its features in endometritis. It was also intended to point out the confusion that has existed in the past about the conditions which have been called endometritis.
To sum up, the modern views on the pathological non-malignant conditions of the endometrium maintain that two main conditions can be demonstrated, the first a true inflammation with microscopical features comparable to those found in inflammatory lesions met with elsewhere in the body, the second a form of hyperplasia corresponding to the endometritis ployposa of Recamier, Olshousens and Matthews Duncan.

In a consideration of a flow of blood from the uterus to which no specific pathological cause may be assigned it is well for one to consider the normal process of menstruation and attempt to determine in what respect or degree this metropathia or essential bleeding has deviated from the normal.

The attainment of sexual maturity or puberty is marked by a number of visible changes in the body, but in the female the characteristic change is the appearance of the menstrual flow from the uterus. The age at which this phenomenon occurs shows many individual variations, but the average for temperate climates is given usually at 14 or 15 years. In the warmer countries the age is earlier,--8 to 10 years,--and in the cold regions somewhat later,--16 years. After this phenomenon appears it occurs at regular intervals of 28 days, more or less, and hence is known as the monthly period, menses, menstruation, or catamenia. The interval is not absolutely regular, and shows many individual variations within limits which may be placed at 20 to 35 days. Certain premonitory symptoms usually precede the appearance of the menses, such as pains in the back or head or a general feeling of discomfort, although in some cases these symptoms are absent. The flow begins with a discharge of mucus which later becomes mixed with blood. The quantity of blood lost
is subject to individual variations, but it may amount to as much as 100 to 200 gms. The flow continues for 3 or 4 days and then subsides. Under normal conditions this phenomenon occurs regularly throughout sexual life,—that is, during the period in which conception is possible. At the forty-fifth to the fiftieth year menstruation disappears permanently, and this change marks what is known as the natural menopause, climacteric, or change of life. The change is sometimes abrupt, sometimes very gradual, being preceded by irregularities in menstruation, and it is not infrequently associated with psychical and physical disturbances of a serious character. Menstruation is a phenomenon of the uterus. The lining mucous membrane, the endometrium, in the period of four or five days preceding the flow, becomes rapidly thicker and its superficial layers are congested with blood, and indeed in places small collections of blood may be noticed. Opinions differ very much as to the change undergone by this thickened membrane during the flow. According to some authors, most of the membrane is thrown off and the blood escapes from the denuded surface mixed with pieces of the membrane. According to others, no material destruction of the membrane occurs, the blood that escapes being due to small capillary extravasations or perhaps mainly to a process of dispedesis. It would seem that the amount of destruction of the endometrium must be subject to individual variations. After the cessation of the flow the mucous membrane is rapidly repaired by regenerative changes in the tissues; the surface epithelium, if denuded, is replaced by proliferation of the cells lining the uterine glands and the thickened edematous condition of the membrane rapidly subsides during a period of
six or seven days. While the escape of blood takes place only from the surface of the uterus, the other reproductive organs—the ovary, the Fallopian tubes, and the external organs—share to some extent in the vascular congestion exhibited by the uterus during the period preceding the menstrual flow. The mucous membrane of the uterus may be said to exhibit a constantly recurring menstrual cycle which falls into four periods: (1) Period of growth in the few (5) days preceding menstruation, characterized by a rapid increase in the stroma, blood-vessels, epithelium etc., of the membrane. (2) The menstruation or period of degeneration (4 days), during which the capillary hemorrhage takes place and the epithelium suffers degenerative changes and is cast off more or less. (3) The period of regeneration (7 days), during which the mucous membrane returns to its normal size. (4) The period of rest (12 days), during which the endometrium remains in a quiescent condition. We know that while menstruation is a normal function of the uterus and an excessive or irregular bleeding indicates a depraved function, it is by no means to follow that the perversion is uterine in origin. We may safely say that except in those conditions in which definite uterine pathology can be demonstrated, the hemorrhage is extra uterine in origin and the uterus is simply an unwitting accomplice to an evil that exists elsewhere. It has been shown that the uterus is the channel of expression, but it is the ovarian function which has primarily gone astray, and which is especially likely to go astray at puberty, when the menstrual process is initiated and at the menopause when it is terminated.

It appears to be clearly demonstrated that the phenomenon
of menstruation is dependent upon a periodic activity of the ovaries. When the ovaries are completely removed menstruation ceases or artificial menopause insues, and the uterus undergoes atrophy. When the ovaries are congenitally lacking or rudimentary, a condition of amenorrhea exists. These facts and the connection of the ovaries with menstruation are further corroborated in a striking way by experiments upon the transplantation or grafting of the ovary. This experiment has been performed upon lower animals (apes), as well as upon human beings. Glass Medical News 523, 1899; Morris Medical Record, 83, 1901. Removal of both ovaries in apes is followed by a cessation of menstruation. Transplantation of an ovary under the skin serves to maintain menstruation but if subsequently removed this function disappears. In humans, an ovary or a piece of an ovary transplanted into the uterus itself or in the broad ligament caused a return of the menstrual periods, which had ceased after surgical removal of the glands, or brought on free menstruation in conditions of amenorrhea.

Many views have been proposed to explain this relationship between uterus and ovary. In the past it was assumed that menstruation in the uterus was connected with the act of ovulation. The later and most widely accepted assumption is that the ovaries form an internal secretion which is given to the blood and lymph and upon reaching the uterine tissues serves to stimulate the mucous membrane to a more active growth. This theory has been elaborated most fully by Fraenkel (Archiv f Gynakologie) 682, 1903) who believes that this internal secretion is furnished by the yellow cells of the corpus luteum; that the ovum is normally discharged two weeks before menstruation,
and the resulting increased activity of the cells of the corpus luteum is responsible for the secretion which stimulates the uterus to the hyperplasia or augmented growth that takes place in the pre-menstrual period. Similar observations backed by more complete experiments are reported by Allen & Doisy (Jour. of The Amer. Med. Assoc. Sept 8, 1923 & Aug. 8, 1925.) To conclude the normal picture, if the ovum is fertilized and implanted the corpus luteum increases in size and its secretion continues to affect the growth of the uterus. If the ovum is not fertilized, the corpus luteum after some days undergoes retrogressive changes, and the hyperplastic endometrium built up during this period degenerates and breaks down with the production of the menstrual flow.

In a consideration of uterine bleeding emphasis may be placed upon the ovarian changes, for these bear very directly on the question of etiology. THERE IS A CHARACTERISTIC ABSENCE OF CORPORA LUTEA AND THE PERSISTENCE OF URRUPTURED GRAAFIAN FOLLICLES. Immediately after menstruation the follicles begin to mature and for some unknown reason one of them outstrips the others to become the presiding ovum of the month. Under the influence of the follicle hormone the endometrium undergoes a slow developmental process—post menstrual—during which no sign of secretory activity is to be seen. The follicle ruptures at about the 13th or 14th day of the cycle and after this the corpus luteum begins to form reaching maturity at the onset of the next menstruation. Under the influence of the corpus luteum hormone which has been given the name Progestin, the development of the endometrium is carried still further with a steadily increasing secretory activity in the
gland epithelium cells. Thus each cycle presents a follicular non-secretory stage and a corpus luteum secretory stage.

Now in cases of functional hemorrhage on the other hand, the follicle does not rupture but continues to secrete its hormone long beyond the normal period so that there is an abnormally great follicular or non-secretory development of the endometrium. The failure of the follicle to rupture means as absence of corpus luteum and of course an absence of any secretory change in the uterine gland epithelium. It is the persistent and excess follicle stimulus which brings about the characteristic hyperplasia of the endometrium (Emil Novak, M.D. Southern Med. Jour. Mar.32)

There is frequently a gross intactness of the mucosa even when bleeding has been profuse and prolonged, suggesting some local biological factor present in the endometrium and increasing the permeability of the blood vessels.

In the Journal of Tennessee Medical, 1933, John C. Burch, M. D., remarks in his article on Endometrial Hyperplasia, to quote, "The endometrium in dependent upon the ovary for its growth and cyclic manifestations and in functional uterine bleeding the ovaries show a characteristic absence of corpora lutea."

One pelvic abnormality is quite commonly found in association with uterine hemorrhage of ovarian origin. There is a uterine hyperplastic endometritis which was first described by (Cullen) Schroeder. This is now regarded as a specific clinical entity which is positively not inflammatory or infectious in origin and which is characterized usually "By a gross proliferation of the endometrium and always by the so
called 'Swiss Cheese' pattern of the glands. If this over-growth is removed by curette it recurs in precisely the same form which may be taken as reasonable proof that the pathology is not local in origin."

Since the normal proliferative activity of the menstrual cycle has been shown to be ovarian in origin and since the above mentioned over-growth is simply an excess of this normal activity it seems equally logical to consider it as a positive indication of ovarian dysfunction.

Its pathology consists of a diffuse, often polypoidal proliferation of the endometrium with a hyperplasia and cystic dilatation of the glands, marked congestion of the vessels, free extravasation into the stroma and extensive endometrial necrosis. The ovaries exhibit characteristic changes in the shape of a cystic degeneration of the follicles and a failure of the formation of corpora lutea and according to Schroeder, the uterine changes and the consequent bleeding arise from this ovarian pathology.

The surface epithelium of the endometrium is high in type, but the epithelium is irregularly distributed because of the areas of disintegration which form so well marked a feature in these cases. The most typical of the characters of the glands is cystic dilation, (Fig. 1), which may be so well marked that the cysts can be recognized with the naked eye. The cystically dilated glands lie mainly in the middle zone of the endometrium. (Fig. 2), and on the whole their distribution is such that where large cysts are present disintegration is slight, though this is not found invariably. The lining
epithelium of the cystic spaces varies in form: on the whole it is high columnar but in places it is cubical and sometimes it is flattened.

The lumina of the cysts contain amorphous debris and large epithelial cells. Some specimens show tortuous glands with stems of connective tissue lined with cylindrical epithelium, giving them a papillary appearance. Frequently an inc. no of glands, they lay very close to each other with the stroma scant between them. Occasionally goblet cells intermingled with the ordinary cylindrical cells and more frequently vacuoles are seen. Stroma is loose in texture in some—dense in others.

On the whole, the endometrium is very hyperemic and the vascularity is best seen in the neighbourhood of the areas of disintegration, although it may not be a well-marked feature in the region of the hyperplastic glands. Around the areas of disintegration there is always intense hyperemia, large dilated capillaries and interstitial haemorrhages being found, and these microscopical features explain the intensely injected appearance which the endometrium offers to the naked eye. Edema of the stroma which results in wide separation of the stroma cells is constantly found and again it is best seen adjacent to the areas of disintegration.

The presence of the hyperplasia of itself does not necessarily seem to be the immediate cause of the bleeding. It has been suggested that local necrotic areas in the endometrium may be the source of the bleeding and it has been mentioned that the possible presence of some local biological factor in the endometrium which increases the permeability of the blood
vessels may be the immediate cause.

The dysplasia of the endometrium results finally in localized areas of thrombotic necrosis with crumbling of the tissues and consequent hemorrhage.

Schroeder found the foregoing factors constantly present in his 53 cases, namely—absent or defective corpus luteum, persisting follicle or follicles, gland dysplasia, and localized necrosis.

Of 15 cases examined by Wilfred Shaw; in every case a cyst was found in the ovaries, in 5 cases more than one was found, the maximum being three. The cysts were invariable unilateral, the opposite ovary was shrunken and its cortex convoluted. On the side of the cyst the ovarian tissue was atrophied the ovary being almost entirely replaced by the cyst. The cysts varied from 2½ inches to one inch in diameter, they were smooth, contained serous fluid and to the naked eye resembled follicular cysts.

The symptoms of the disease are very typical. In almost all cases the patients come in complaining of continuous vaginal hemorrhage. The hemorrhage is very frequently preceded by a period of amenorrhoea varying between 5 and 12 weeks and continuous vaginal hemorrhage for 3-8 weeks or more. The hemorrhage may be so severe as to produce a secondary anemia.

The pelvic physical signs of the condition are simple; namely a uterus which is smooth, may be a little enlarged, and a unilateral cystic ovary, the vaginal hemorrhage is usually not excessive and the blood is dark and fluid.

With young patients the complexion is very characteristic as there is a slight malar flush while the skin of the face and
the mucous membranes are pale.

In a large number of cases the history of bleeding with the absence of any gross pathology allows the diagnosis to be made with approximate accuracy. The irregular bleeding of young girls is generally due to ovarian dysfunction but with increasing age the frequency with which other factors operate makes the diagnosis more difficult. As the bulk of cases fall between the ages of 40 and 50 when cancer and fibroids compete so largely, the need for an immediate investigation in such patients is especially urgent and the same applies to bleeding beginning for the first time after menopause when malignancy—usually in the cervix—more rarely in the uterine body or ovary is the most frequent single factor present.

When physical examination fails to reveal the presence of an adequate explanation of the bleeding such as fibromyoma, cervical cancer, a polypus projecting from the cervix or an inflammatory mass in the tubo ovarian region, it may be laid down as a rule that curettage is the first step in the diagnosis.

Bleeding in the teen is the only exception to this rule and in such cases treatment may be begun forewith on a clinical diagnosis.

The endometrium in cases of this type presents a very characteristic picture spoken of as hyperplasia of the endometrium. The chief features are the so called "Swiss Cheese" pattern of the glands and the absence of any secretory activity of the glandular epithelium. There is usually no intermenstrual discharge and on histological examination of the scrapings there is not the slightest resemblance to cancerous tissue. The condition is distinguished from carcinoma by the intense hyperemia.
and purplish color of the pedunculated processes projecting downward toward the internal os and by the absence of purulent discharge or of any invasion of the wall of the uterus.

In the absence of any gross uterine pathology to explain such cases as occur within a reasonable short interval after the menopause an ovarian cause has been invoked either in the nature of a temporary rejuvenescence of the organ or of structural degeneration of dormant follicles. When this occurs about the only presenting symptom is a continual bleeding, occasionally profuse and not accompanied by discharge and occurring months to a year after the menopause has been firmly established. Physical examination here, in the majority of instances, reveals even less than that occurring at puberty. There are no symptomatetic findings other than the bleeding and physical and psychical changes that are frequent at this period of life. Experiments performed in 1931 upon a castrated woman with the use of the hormones contained in the uterine of pregnant women succeeded in reviving the function of menstruation. Thus one can assume that the rejuvenation of the ovary, perhaps under the influence of a stimulus from the pituitary gland has again, after menopause, caused the uterus to take up a temporary normal functional roll.

The infrequency with which in the literature we now find reference to such conditions as chronic metritis, sub-involution, fibrosis uteri...terms which with their implication of an inflammatory and infective etiology were common 20 years ago...Wilfred Shaw found no pathology justifying the use of such terms as chronic metritis or subinvolution.
CASE REPORT

Patient---Mrs. G. Y. S.  Hospital Number---#37,249

The patient, a white married female, first entered the University of Nebraska Hospital at the age of 19 years, complaining of profuse, irregular uterine hemorrhage. Her menstrual history is as follows: the menses began at 12 years of age and during the first year the periods were irregular every two to three months with a flow which was not at any time excessive, lasting about two weeks. At 17 years of age, the patient experienced a period of amenorrhea for a duration of five months, followed by a three months flow. At 18 years of age, the patient again had a prolonged three months flow and at this time she experienced considerable weakness and was confined to bed. In July 1931, prophylactic curettage was done and the patient was free from continuous hemorrhage for a period of one month. Following this lapse the hemorrhage re­curred and December 12, 1931 she entered the University Hospital for the first time with the above complaint, complicated by pain in the right lower quadrant and a palpable mass in the right adenexia. Her blood picture at this time was as follows:

12-12-31  Hbg. 30%  Reds- 3,000,000  and whites--6,600.  On
12-19-31  Hbg. 55%  Reds- 4,304,000  and whites--12,000.

On the basis of lower quadrant pain and a mass in the right adenexia she was operated upon and the following corrections made: Right Salpingectomy and partial left, Right Oophorectomy and partial left. The ovaries were found to be hen eggs size and cystic. A small portion of the left tube and ovary were allowed to remain. The operative diagnosis was right hydrosalpinx, ovarian cysts bilateral, and paraovarian cysts left.
The patient returns to the hospital again at the age of 22 with practically a repetition of her previous complaint: Lower left quadrant pain and a palpable mass in the left side. Her blood picture on entrance was: Hbg. 96% Reds--5,100,000 and Whites--14,200.

For the last four months previous to entrance she had experienced a constant flow with severe hemorrhage about once a month.

Knowing the condition of the remaining portion of the ovary it was decided to operate and perform a complete hysterectomy and Salpingoophorectomy left, as it was felt that any glandular therapy that might be resorted to would be entirely inadequate to control the uterine hemorrhage as so little functional ovary remained to be affected by the therapy.

At operation the uterus was found to be, on half section, about one and a half times normal size, the muscular wall about one centimeter thick and within normal limits, but the endometrium was about six times thicker than normal, highly macroscopically cystic and of a typical "Swiss Cheese" appearance, with multiple polypoidal masses projecting downward toward the internal Os. The ovary, that small portion remaining, (about one-third of the normal amount) had become cystically enlarged to about the size of a large orange, composed of five large cysts incorporating several small ones. Macroscopically it was found that there was no functional ovarian tissue remaining. (See Fig. 1 and 2).
Figure 1. Half section of the uterus of the hystereotomized patient, hospital number 37249, showing the thickened endometrium and the characteristic *Swiss Cheese* appearance of the glands. (Actual size.)
Figure 2. Half section of the left ovary of hospital patient number 37249 showing the cystic dilatation. No functional ovarian tissue remaining. (Actual size.)
Figure 3. A sectioning of a uterus showing the polypodial overgrowth of the endometrium. (Sohroeder archiv f gynek.)
Figure 4. Microscopic section of hyperplastic endometrium showing the cystic formation in the middle zone of the endometrium. Hospital number 37249. (Magnification 25x)
When functional hemorrhage is so severe as to impel the patient to seek medical advice the plan to be followed depends upon several factors and especially upon the age of the patient, and the severity of the bleeding. When the bleeding is alarming, curettage offers quickest and immediate relief. At times it must be preceded by transfusion. When less severe and when the patient is young so that the probability of cancer need scarcely be considered, efforts at organotherapy are justifiable—altho in the past most always unsuccessful.

When the patient of middle life presents herself with bleeding for which no obvious anatomical cause can be found, curettage is the first step and clearly indicated. For it not only checks the bleeding at least temporarily but it establishes the diagnosis and eliminates cancer. Once the diagnosis is made by the finding of the characteristic hyperplasia the further treatment of the patient at or near the menopausal age is simple. Here is found the most brilliant application of radio-therapy in the field of gynecology. Either radium or x-ray in adequate dosage yields virtually 100% of cures by the induction of the menopause, for at this age the prevention of the reproductive function need rarely be considered.

When bleeding recurs after curettage in young women a serious problem arises, for here destruction of the reproductive function would be a calamity. The technique of radio-therapy has been so developed that by careful small dosage permanent sterilization can be avoided as a rule—with only temporary cessation of function. But there are women who are extremely sensitive to the effects of radiation so that even very slight
dosage may bring about permanent amenorrhea and sterility and so most gynecologists and radio therapeutists are agreed that radio-therapy in young women should be only a last resort. Here the only alternative in the past has been a repetition of the curettage, perhaps several times depending on the severity of the recurrences. It is this group of cases—functional hemorrhage in young girls—which has constituted the most serious problem.

A new and welcome measure is the use of an anterior pituitary lutenizing substance obtained from the urine of pregnant women. Suffice to say that the idea behind this treatment is to activate lutenization in the ovary by the injection of the anterior pituitary lutenizing hormone. As the lack of lutein is the chief factor in this disorder this seems rational. Emil Novak has employed this plan in the treatment of more than 100 cases, many of them of the recurring type with often the history of one or more curettages. Most of these patients were young so that radio-therapy would have been undesirable. To quote Emil Novak: "While not infallible, the bleeding in all except a small proportion of cases has been checked by the intramuscular injection of usually 200 rat units of this preparation on from 2 to 5 successive days. In bleeding of the periodic type the injections are begun with the onset of the period. —Unfortunately the effect of treatment appears to be transitory, that is, limited to that particular attack but with repeated injections there is a tendency in very many of these cases toward a readjustment of the endocrine balance so that after a period of time menstruation may again become normal."

This plan was suggested in 1931 on the theory that if
progestin were available it should be possible to convert the hyperplastic endometrium into a functional pre-gravid one thus completing the cycle. This can actually be accomplished as has been shown by Clauberg in an experiment on a castrated woman--large and prolonged dosage with folliculin produced a typical hyperplasia of the endometrium but further injections of progestin converted the latter into a typical secretory one corresponding to the normal premenstrual phase.

Unfortunately this treatment due to lack of available material is still largely in the experimental stage, but the promising success that experimenters have had with organotherapy so far, promises well for future work on the basis of endocrine dysfunction. In as much as organotherapy is largely a new and uncharted field in the science of medicine, there is much conflicting data and poorly compiled statistics as to results of recent experiments.

This brief on recent treatment can be merely suggestive and cannot hope to do any more than show a possible field for future therapeutic developments.
Metropathia Haemorrhagica may be defined as a condition of irregular and excessive uterine hemorrhage in which there is no demonstrable pathology locally present to sufficiently explain the condition.

2. This condition may occur at any age from puberty onward and is found characteristically between the ages of 40 and 50.

3. These cases have in the past been labeled with such terms as epimenorrhoea menostaxis, metorrhagia, and essential uterine bleeding although indicating the type of the irregular hemorrhage offer no explanation as to the cause of the abnormality and fail to throw any light on the causative factors.

4. Etiology on the basis of endometritis; instigated by Ruge in 1879 as a result of an investigation into the micro anatomical features of specimens of the endometrium removed by curettage of the uterus, has since been discarded due to the inability of later investigators to demonstrate a bacterial flora on which to base an infective factor.

5. Cases of irregular and excessive uterine bleeding may be divided into two classes (1) those in which the uterus is the seat of tumors, fibromyoma, mucous polypi and malignant disease or retained fragments of placenta (2) those in which such a gross pathology is absent and where instead there is nothing more than changes in the endometrium, usually of a proliferative nature, with commonly, in addition, some general and uniform overgrowth of the fibro muscular wall of the uterus.

6. The earliest investigations on the pathological conditions of the endometrium followed the introduction of the curette into gynaecology by Recamier, for with the help of the curette,
fungous and granulation like pieces of endometrium were removed and although the specimens on histological examination showed little if any departure from the normal the conclusion was reached that the fungous condition of the endometrium was the result of an inflammation. In 1882 Brennecke suggested that the hyperplastic endometritis type of Ruge was not the result of an inflammation but was a true hyperplasia and went so far as to state that THE CHANGES IN THE ENDOMETRIUM WERE THE RESULT OF AN OVARIAN ABNORMALITY.

7. It is interesting to note that the origin of the modern interpretation depends upon the observations of Hirschmann--Its success was determined by the scientific method in which the investigations were made. For the first time the structure of the endometrium at the various phases of the menstrual cycle was described and with this as a standard the variations from the normal could be recognized and their real significance appreciated.

8. The publications of Schroeder on the changes in the endometrium during the menstrual cycle, on the whole show complete agreement. He also confirmed the work on endometritis, and correlated the menstrual disturbances with changes found in the endometrium.

9. In a consideration of an excessive and irregular flow of blood from the uterus to which no specific pathology can be assigned it is well for one to consider the normal and from this attempt to determine to what respect or degree this Metropathia Haemorrhagica has deviated from the normal.

10. The uterus may be said to be the channel of expression but it is the ovarian function which has primarily gone astray and
this is especially likely to occur at puberty when the menstrual process is initiated and at menopause when it is terminated.

11. It appears clearly demonstrated that the process of menstruation is dependent on a periodic activity of the ovaries, for when the ovaries are completely removed menstruation ceases (artificial menopause) and the uterus undergoes atrophy. When the ovaries are congenitally lacking a condition of amenorrhea exists. When in a castrated case a portion of ovary is transplanted under the skin or into the uterine cavity the menstrual function is again resumed. Showing that changes in the uterine mucosa are directly dependent upon the ovarian control thru the blood stream.

12. The most widely accepted assumption of ovarian control is that the ovaries form an internal secretion which is given to the blood and lymph and upon reaching the uterus serves to stimulate the mucous membrane to a more active growth. This theory has been elaborated most fully by Fraenkel (archiv f Gyanakologie 682,1903) who believes that this internal secretion is furnished by the yellow cells of the corpus luteum; that the ovum is normally discharged two weeks before menstruation and the resulting increased activity of the cells of the corpus luteum is responsible for the secretion which stimulates the uterus to the hyperplasia or augmented growth that takes place in the premenstrual period.

13. In a consideration of uterine bleeding emphasis may be placed upon the ovarian changes for these bear very directly on the question of etiology: THERE IS A CHARACTERISTIC LACK OF CORPUS LUTEA AND THE PERSISTENCE OF UNRUPTURED GRAAFIAN FOLLICLES.
14. For as shown under the influence of the follicular hormone the endometrium undergoes a slow developmental process Post menstrual—during which time no secretory activity is seen. The follicle ruptures about the 14th day and after this the corpus luteum begins to form reaching maturity at the beginning of the next menstruation. Under the influence of the corpus luteum hormone (PROGESTIN) the development of the endometrium is carried still further with a steadily increasing secretory activity. BUT in functional hemorrhage the FOLLICLE DOES NOT RUPTURE, and the uterine mucosa remains under the influence of the non-secretory—follicular hormone. It is this persistent and excess follicular stimulus which brings about the characteristic hyperplasia of the endometrium.

15. One pelvic abnormality is quite commonly found in association with uterine hemorrhage of ovarian origin. There is a uterine hyperplastic endometritis that was first described by Schroeder. This is now regarded as a specific clinical entity which is positively not inflammatory or infectious in origin, and which is characterized by gross proliferation of the endometrium and by the so called SWISS CHEESE pattern of the glands. If this overgrowth is removed by curette it recurs in precisely the same form which may be taken as reasonable proof that the pathology is not local in origin.

16. The presence of hyperplasia itself does not seem to be the immediate cause of the bleeding. It has been suggested that local necrotic areas in the endometrium may be the source of the bleeding and some local biological factor in the endometrium which increases the permeability of the blood vessels may be the immediate cause.
17. Wilfred Shaw found in 15 cases examined by him that in every case a cyst was found and in 5 cases more than one. The cysts varied in diameter from 1 to $2\frac{1}{2}$ inches, were smooth and contained serous fluid.

18. The symptoms of the disease are very typical. In almost all cases the patient comes in complaining of continuous vaginal hemorrhage. The hemorrhage very frequently preceded by a period of amenorrhoea. The pelvic physical signs are simple, namely, a uterus which is smooth, and may be a little enlarged and an unilateral cystic ovary. The vaginal hemorrhage is usually not excessive and the blood is dark and fluid. The complexion is pale with a malar flush to the cheek.

19. The irregular bleeding of young girls is generally due to ovarian dysfunction. But with increasing age between 40 and 50 when cancer and fibroids compete so largely the need for an immediate investigation is urgent and likewise after the menopause.

20. It may be laid down as a rule that curettage is the first step in a differential diagnosis. Bleeding in the teens is the only exception.

21. On histological examination of the scrapings there is not the slightest resemblance to cancerous tissue. The condition is distinguished from carcinoma by the intense hyperemia and purplish color of the pedunculated processes projecting downward toward the internal Os and by the absence of any purulent discharge or any invasion of the walls of the uterus.
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