Menorrhagia due to endocrine factors

Albert E. Freed
University of Nebraska Medical Center

Follow this and additional works at: https://digitalcommons.unmc.edu/mdtheses

Part of the Medical Education Commons

Recommended Citation
Freed, Albert E., "Menorrhagia due to endocrine factors" (1939). MD Theses. 744.
https://digitalcommons.unmc.edu/mdtheses/744

This Thesis is brought to you for free and open access by the Special Collections at DigitalCommons@UNMC. It has been accepted for inclusion in MD Theses by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.
MENORRHAGIA DUE TO ENDOCRINE FACTORS

Senior Thesis presented to the College of Medicine, University of Nebraska.

Albert E. Freed
Omaha, Neb. 1939
# TABLE OF CONTENTS

1. Introduction

2. Normal interrelation of hormones  
   Nomenclature of hormones

3. Findings in normal menstruation

4. Pathology in menorrhagia  
   Methods of investigation  
   Endometrial hyperplasia  
   Cystic ovaries  
   Irregular shedding and ripening of endometrium  
   Blood content of hormones

5. Cause of Bleeding  
   Cause of bleeding in normal menstruation  
   Endometrial hyperplasia  
   Failure follicle to rupture  
   Vessel change  
   Novak's bleeding factor  
   Irregular ripening and shedding of endometrium  
   Progestin

6. Diagnosis

7. Treatment  
   Hygienic measures  
   Uterine stimulants  
   Measures to decrease the coagulation of the blood or permeability of vessels  
   Snake venom  
   Vitamin C  
   Endocrine  
   Estrin  
   Insulin  
   Corpus luteum  
   Thyroid  
   Urine Prolan  
   Antuitrin S  
   Follutein  
   Antophysin  
   A.P.L  
   Urine retention enema  
   Pregnancy blood injection  
   Anterior pituitary extract  
   Mammary gland extract  
   Removal or destruction of endometrium  
   Roentgen or radium therapy  
   Surgical procedures upon ovary or uterus

481036
INTRODUCTION

Menorrhagia may be defined as a cyclic hemorrhage producing an abnormal loss of blood. The flow may be increased in duration or amount but the cyclical character is maintained. The hemorrhage occurs from an organ which normally manifests its physiologic activity by cyclical periods of bleeding so that often an exact differentiation of normal and abnormal proves difficult. The condition may have been present over a long period of time without having produced marked results, or again it might be sudden in onset and sufficiently profuse as to threaten the patient's life.

A thorough examination to eliminate any pelvic pathology or the presence of other disease, will show many of these cases of excessive bleeding to be due to endocrine disbalance. It is with this type of condition that this paper will be concerned.

Uterine bleeding of endocrine origin may occur at any age between puberty and well-established menopause. It is, however, most frequently encountered at the beginning and decline of menstrual life when the secondary phase of the ovarian cycle, luteinization, is most likely to be defective or absent. At puberty the bleeding may result from the early appearance of the pituitary secretion before the ovary is capable of its balancing function. In pre-menopausal patients, it is believed due to a gradual inability of the ovary to maintain its functional life, while in those patients between these extremes, many possible factors may be responsible, cysts and tumors of pituitary or ovary active in hormonal secretion, often producing the disbalance.
Normal inter-relation of hormones

To correctly understand the role of hormones in the cause and treatment of functional uterine bleeding it is necessary to know their action and inter-relation in the normal menstrual cycle.

For the completion of a satisfactory menstrual cycle, Kane as well as other investigators believe that four hormones must be present, must be properly balanced in quantity and must make their appearance in the proper sequence.

It has been shown recently by Zondek and Ascheim in Germany and Smith and Engle in this country that the anterior pituitary gland plays a dominating role or is the "motor-control" in menstrual and reproductive cycle of women.

From the anterior lobe of the pituitary gland come the prolans A and B, sometimes known as Rho I and Rho II. Physiologists differ as to whether there are two distinct forms of prolan or one substance with two actions or just a quantitative difference of one. The belief that there are two distinct elements is, however, more commonly accepted. Through the prolans, the anterior pituitary is the stimulator or energizer of the ovary. The ovary produces two hormones, oestrin and progestin, which in turn act on the endometrium and uterine muscle.

The function of prolan A is to stimulate the growth, development and maturation of the primordial follicle up to the Graafian follicle stage inclusive. It is called the sex-stimulating hormone.

Prolan B does not become active until the Graafian follicle
has been formed. When the follicle ruptures, it causes luteinization of these cells, and is, therefore, known as the luteinizing hormone. Prolan B has a luteinizing action on the primordial cells, stops their development and thereby prevents the formation of more than the one Graafian follicle which is needed. Prolan B is antagonistic to prolan A at this point, but is synergistic in that by changing the theca into lutein cells, it completes the process of forming the corpus luteum.

The ovarian follicles, during their development, are forming in the follicular fluid a hormone formerly known as the female sex hormone. This rather general term has been supplanted by the names folliculin or oestrin or theelin. Oestrin causes re-menstrual congestion, vascularization and hypertrophy of the endometrium. It also has the property of stimulating contractions of the uterus and producing growth, greater motility and increased blood supply in all the the accessory genital organs, especially the vagina, uterus and mammae.

With the rupture of the Graafian follicle, the lutein cells formed by prolan B constitute the corpus luteum. This structure continues to secrete a small amount of oestrin, but its principal function is the elaboration of the hormone progestin, which is concerned chiefly with the secretory phase of the endometrium.

Progestin is antagonistic to prolan A in that it aids in inhibiting the development of primordial follicles. It is antagonistic to oestrin in that it checks the process of endometrial hypertrophy and prevents uterine contractions; when it has the
controlling influence it tends to keep the action of oestrin in obedience, or even force its excretion in the urine. A third property of progesterin is the sensitization and preparation of the endometrium for the nidation of the ovum in case fertilization has occurred.

However, it must be remembered because of its clinical importance that progesterin can produce none of the changes specific to it unless the endometrium has been primed with oestrin. The influence of oestrin on endometrium followed by progesterin stimulation is a one-two type of action and in this respect the hormones are synergistic.

The presence of a fertilized ovum is necessary for the persistence of the corpus luteum. An unfertilized ovum is absorbed in three or four days. The consequent retrogressive changes in the corpus luteum stop the supply of progesterin. The growth of the ovarian follicles has been stopped by prolan B and progesterin, thus preventing the formation of oestrin. In the absence of oestrin there is no stimulation of endometrial hypertrophy and as there is no longer a supply of progesterin to maintain this condition, the endometrium degenerates and the normal hemorrhage of menstruation occurs.
Findings in normal menstruation

Cyclic changes of the endometrium were described as early as 1896 by Westphalen, by Hitzchmann and Adler in 1908, and Schroeder and Novak in 1915 established the concept of the various phases of the cycle which in general is accepted today. Briefly stated, the changes in the endometrium have been classified in four phases, (1) the post menstrual phase, (2) the proliferative phase, which was previously described by Novak and others as "interval" endometrium, (3) the secretory or premenstrual phase and (4) the menstrual phase.

According to G. W. Bartelmez, termed one of the greatest authorities on this subject, menstruation is a bloody discharge associated with necrosis of uterine mucosa, recurring in the absence of pregnancy, at intervals of three to five weeks. Statistical evidence now shows that the 28 day cycle is average. In other words if one cycle happens to be 28 days the next will probably be longer or shorter. The discharges coagulates slowly, incompletely or not at all.

The features common to menstruation shown by the mucosa are:

1. Extravasation of blood
2. Superficial necrobiosis
3. More or less leukocytic infiltration and after first day, small glands cells and characteristically dense stroma.

According to Bartelmez, while it is probable that there is some loss of tissue in the course of every period--ovulatory and anovulatory, it is significant that histologically normal areas can be found from the first, second and third day of the flow in
uteri which have an intact epithelium apparently not recently re-
genenerated.

Before the end of menstruation much of the denuded surface is
again covered by epithelium. Most recent observers agree that
the cells migrate out radially from the mouth of the glands, the
adjacent sheets meeting to restore the endometrial surface as Von
Herwerden first showed in the new epithelium spreading beneath
the "menstrual-clot".

It has been suggested that the menstrual necrosis is due to a
vasoconstrict such as is manifested post-partum. Bartelmez finds
wide variation in the appearance of the spiral arterities at
different levels of the mucosa and usually not uniformity in the
arteries of any given specimen. Various conditions are listed which
suggest that these vessels conduct little or no blood; leading to
the conclusion that the ischemia is due to the constriction of the
vessels in the myometrium.

Anovulatory cycles have also been demonstrated by adequate
histological study for various specimens of monkeys. There are
at least 17 reasonably satisfactory human cases in which menstrua-
tion appeared at the expected time but neither ovary contained a
corpus luteum which could be ascribed to the immediately preceding
cycle.
Pathology in menorrhagia

a. Methods of investigation

Since the endometrium closely reflects the functional activity of the ovaries a histological examination of this tissue is considered of utmost importance in all cases of abnormal functional uterine hemorrhage.

Novak emphasizes the importance of microscopic study of specimens of the endometrium in a study of menstrual disorders for this tissue he says is a "mirror of ovarian activity" and more can be learned from it than from blood and urine hormone studies.

The first means of studying uterine endometrium tissue in living subjects developed in 1850 when Recamier designed the curette to remove "fungoid and granulation like pieces of tissue" from the uterine cavity. He thereby first provided a means of studying this tissue which changed completely the older concepts of endometrial disease. The use of curettage as well as uterine and ovarian specimens removed at operation have enabled investigators to correlate uterine findings both normal and pathological with the inter-relations of endocrine of both ovary and pituitary.

The older investigators and writers as Rokitansky, Scangani 1863 Pozzi, Olshausen (1875), Ducan 1879 and Ruge 1879 all believed the inflammatory condition of the endometrium accounted for the histological changes seen and offered this as an explanation of the various types of abnormal endometrial bleeding associated.

That the "hyperplastic endometritis" type was not due to an inflammatory lesion was first proposed by Bremecke (1882) and
corroborated in rapid succession by De Senet 1884, Schmal 1890 and Cullen 1900. These authors found that the hyperplasia of the endometrium associated with functional bleeding was a distinct entity in no way associated with influence of the mucosa.

A group of men including Doderlein 1896 Pfannevistsiel, Bumm and Menge then proved by bacteriological investigation that these tissues were free of bacterial invasion.

In 1907 Hitschmann and Adler made classical contributions on cyclical changes occurring in endometrium. Schroeder in 1912 made brilliant investigations upon the relationship of the normal endometrium cycle to the ovarian cycle.

Again in 1919 Schroeder made studies of hyperplastic changes of uterine mucosa. He confirmed the work of earlier groups of writers, that hyperplasia of endometrium was not of an inflammatory nature. He further described its histological features and correlated it with occurrence of graafian follicle cysts in the ovary. He suggested from his findings that it was due to the persistence of follicle or lack of corpus luteum formation. Burch, Williams and Cunningham (1931) have supplied evidence through their investigative animal experiments that hyperplasia endometrium result of unopposed estrin effect. Mice and rats are the type of animals usually used.

Curettage under anesthesia is by far the most desirable method of obtaining endometrial tissue by the necessary hospitalization is of disadvantage in making extensive use of this operation.

For this reason a number of methods which can be more easily employed have been developed to be used in obtaining small fragrance
of uterine mucosa for examination.

Burch and Klinger made use of a copper tube to secure pieces of endometrium. Novak and also Tamis employ suction with curettage and have devised special annulas for this purpose. Howard Kelley in Stanford Clinic uses a small curettage with a tip 2 by 3 mm which is constructed with a thin shank so that it can be readily bent. No anesthesia is employed but at times one half grain of codeine sulfate is given by mouth before operation. Patients are placed in the lithotomy position, the cervix is exposed with a bivalve speculum cleaned with gauze sponges, and painted with an antiseptic preparation such as 5% picric acid solution. It is then grasped with a tenaculum forceps and a sound is passed into the uterine cavity. Preliminary to introducing the sound the cervical canal may be dilated with Hegar dilators and then an attempt made with curettes to obtain specimens from anterior, posterior and lateral walls of uterus. Tissue obtained is put in formalin and mounted in paraffin. Sections are routinely stained with eosin-hematoxylin while special stains as Meyers Mucicarmine or Unna Poppenheim methyl green pyronin stain for plasma cells are employed when indicated.

When the pieces are small, they may give a wrong impression owing to the variability of the endometrial reaction in different sections of uterus. Small carcinomas might in this way be overlooked. However, in most instances of uterine bleeding a correct diagnosis may be made this way as was shown by Dr. Hoffman who obtained biopsy specimens from patients just before they were subjected to
hysterectomy and when the entire endometrium was subsequently available for comparison again Fluhmann compared the use of small biopsy specimens of uterine mucosa to that of tissue obtained from an extensive curettage under anesthesia or from complete specimen of the uterus. The series represents a group of women with uterine bleeding in whom the condition was considered sufficiently serous to warrant hospitalization. It was found that there was a similarity in the percentage of various findings in both groups, thus offering further efficacy of biopsy specimens.

Since direct methods, rather than endometrium changes, are used by some investigators to demonstrate hormone, a procedure for the demonstration of estrin in blood may be considered a part of investigating methods.

C. H. Fluhmann employs a technic which depends on the importance of small amount of untreated serum into sprayed mice. A positive results indicated by the production of a "mucification" of the vaginal mucosa. This method may be applied to quantitative studies provided a sufficient number of test animals are used. Examination of 80 specimens from 46 women at different stages of cycle showed in this series a maximum condition of estrogenous substance at middle of the interval. A second rise occurred at the time of flow, and it was diminished just before and just after menstruation. These facts can be used to detect abnormal amounts of estrogenous substances at any part of the cycle.

b. Endometrial hyperplasia

Burch and McCellan of Vanderbelt University have shown by experi-
mental work that primary and secondary ovarian failure are capable of producing the same endometrium lesions. The clinical correlation of symptoms and endometrium indicates that there is one single endometrial lesion always associated with a specific menstrual disorder, however, there is a tendency for some to predominate. An example of the inconsistency of disorder and finding is the high incidence of reports associating hyperplasia and bleeding, while routine curette specimens on endometrium have demonstrated marked hyperplasia with no associated bleeding.

Endometrial hyperplasia is the pathological finding most commonly found in conditions of excess functional bleeding. This work done in demonstrating this fact has been only recent--mostly in the past seven years. Dr. E. Murray Blair says "that even six years ago the entity endometrial hyperplasia was little known to the majority of physicians". Yet, in 1934 in Vancouver General Hospital alone this finding was reported from pathology department some 200 times.

Now according to Traut and Kuder, about 85% of functional bleeding has come to be classified as due to hyperplasia of endometrium. Novak makes the statement "histologic examination of endometrium in cases of functional bleeding almost always reveals the picture designated as hyperplasia of endometrium".

Schroeder (1918) was one of first to note the frequency of occurrence of endometrial hyperplasia in bleeding conditions and by his experiments was able to confirm the works of earlier writers that hyperplasia of endometrium was not of an inflammatory nature.
He further described its histological features and correlated it with the occurrence of Graafian follicle cysts in ovary, suggesting that it was due either to the persistence of the follicle or lack of corpus luteum formation.

The statistical finding however, may for many reasons vary. Some investigators claim findings of hyperplasia in 85% of cases of bleeding. Shaw reports the findings in 50% of cases, while Henderson says that hyperplasia is only present in 33% of cases. However, there does seem to be a general agreement that a large percent of pubescent and adolescent cases are due to hyperplasia according to Kauffman. Heynemann found it in 80% of 31 cases of juvenile bleeding.

In eleven cases at Stanford clinic where continuous bleeding followed the usual cycle, the endometrium was examined and following findings reported: hyperplasia 3 cases, endometritis 2 cases, and normal endometrium 2 cases, and prolonged defective desquamation in 2 cases showing presence of collapsed glands—evidence of secretion, normal secretory glands—shrunken stroma and even round cell infiltration.

Fluhmann shows in series of 74 biopsy specimens from 54 patients with abnormal bleeding listed the following finds:

1. Hyperplasia of endometrium in 22
2. Endometritis 5
3. Normal appearing endometrium corresponding to time cycle 19.
4. Atypical endometrium for period cycle 2
5. Prolonged defective desquamation 2
6. Anovulatory menstruation—some bleeding occurred while the endometrium showed histological changes of "estrogen phase".
In two series of cases in 1929 and 1936 Fluhmann reported hyperplasia of endometrium occurring in 54% of 1929 groups and 40% of 1936 series. The diagnosis of endometritis was made in 8% of 1924 cases and 9% of cases in 1936. The rest of cases showed no definite pathological lesions.

Witherspoon after extensive microscopic study on endometrial tissue reported that histopathological characteristics of endometrial hyperplasia are very distinctive. Grossly the endometrium may be thickened, overgrown or polypoid. The microscopic picture represents hyperplasia of glandular and stromal elements. Lack of uniformity of the glands, the so called "Swiss cheese pattern" is characteristic. Large dilated, even almost cystic glands are adjacent to small narrow non-tortuous ones. The nuclei of the glandular epithelium are heavy and solid. The cellular structures are similar to the epithelial features of the rest of interval stage of the menstrual cycle. The stroma is abundant, dense and compact, with frequent mitosis of these cells. In some sections the glandular elements predominate, while in others the reverse is found, proliferation of stromal features.

Hyperplasia is considered to be a manifestation of prolonged and unopposed effect of Graafian follicle hormone, estrin, upon mucosa uterus. This effect is apparent in curettage specimens in overgrowth of various elements composing endometrium, both glandular and stromal. It is also however, characterized by a complete absence of any of evidences of secretion, such as presence of glycogen etc., which have come to be recognize as the effect of
corpus luteum hormone on the endometrium. In other words, hyperplasia of endometrium may be considered to be the outcome of hyper-estrin or Graafian Follicle effect without the formation of a corpus luteum with its ripening and secretory influence. It is therefore, distinctly an abnormality of the proliferative or follicular phase.

c. Cystic ovaries

In 31 cases at Vancouver Hospital, where menorrhagia necessitated hysterectomy, most cases being near the menopause, Dr. Blair reports the following findings: (each uterus in this group was a normal uterus with a hyperplastic endometrium) 11 cases showed single or multiple cysts, predominately of follicular type.

In his observation on uterine changes, Franks has found that in the early stages of adult menorrhagia, the patients uterus is normal. Finally, in the course of years, the uterus enlarges symmetrically. It is at first boggy but later becomes firm and fibrous. Curettages show hyperplastic, polypoid or cystic endometrium. The ovaries are normal or may be "microcystic".

An interesting finding of pathologists in another series at Vancouver, was not less than 10 luteal cysts in 81 cases of hyperplasia and excess estrin. Such a finding is not compatible with the accepted theory of hyperplasia and hyperestrinism. Blair believes hormones to be found in conjunction with multiple follicular cysts. According to the Fluhmanns it may be that there is so great a preponderance of oestrin in the system by virtue of prolonged retention cysts in the ovaries that the occasional
ovulation and resulting luteal body and progestin formation had little or no effect on the endometrium. These ovaries probably ovulate on occasion, hence, the unusual picture of a corpus luteum in the presence of hyperplasia.

K. Tietze discusses follicle persistence with glandular hyperplasia. His discussion is based on observation in 466 cases treated in the clinic at Kiel in the last 10 years. He stresses the higher incidence of the disturbance at the beginning and endometrium of the period of sexual function and also the fact that in most cases of glandular hyperplasia, disturbance in menstruation exist before the onset of the disease. He discusses cases of short or prolonged hemorrhage with the clinical peculiarity of glandular hyperplasia and follicle persistence.

He states that in all but one of the cases, where histological examination was possible, large cystic granulosa-bearing follicles were found in the ovaries.

d. Irregular ripening and shedding of endometrium

Traut and Kuder believe that there are other clinical entities with a corresponding histological picture in the endometrium responsible in functional bleeding, than just the picture of endometrial hyperplasia so often described. They are believed to be of a similar nature in so far as they are probably the result of ovarian or other glandular unbalance but yet are distinct from endometrial hyperplasia. These two metropathies are: irregular shedding of endometrium, and irregular ripening of decidua.

The first condition they describe, irregular or incomplete
shedding of endometrium is an aberration of the secretory or corpus luteum phase.

In 1924 Pankaw reported 3 cases of menorrhagia in women whose previous menses had been quite normal, but who had experienced excessive and prolonged menorrhagia during the period just prior to admission to the clinic in Duesseldorf. Curettage of the uterus in these women produced an endometrium without an epithelial surface layer, but with compact, infiltrated stroma and collapsed glands. As an explanation, Pankow stated that he thought, that these cases must represent a delayed regeneration phase. This is the first reference in the literature to this syndrome of irregular shedding.

Kaufmann and Hoeck, in describing a large series of patients (147) suffering with various forms of endometrial bleeding, referred to one group of 6, which, from their descriptions of the clinical findings as well as the appearance of the endometrium indicate to Traut and Kuder that these patients were suffering from irregular shedding of the endometrium or a closely allied difficulty.

Baniecki, in 1928, described 32 cases of irregular shedding of the endometrium from a series of 465 curettage specimens (an incidence of 7%).

Fluhmann on 11 cases of functional bleeding at Stanford clinic reported besides hyperplasia endometrium—a typical type tissue, the condition of definite desquamation (irregular shedding) in two cases showing areas of active tissue intermingled with shrunken stroma and collapsed glands.
In the year 1935 Traut and Kuder had 11 patients from a series of 97 who have suffered from functional bleeding of the endometrium, who seem to fall into this category, an incidence of 10%, showing that it is not a rare condition. These patients covered an age range of from 23 to 50 years, the majority of the patients being between the ages of 23 and 40 years.

These women all gave a history of having had a normally regular menstrual periods until they came under observation because of a prolonged and profuse menses or of recurrent bleeding immediately following what was supposed to have been a normal menstrual period. Duration of the bleeding was from 10 to 43 days, in the majority 8 to 14 days. Estrogen determinations on the blood of 4 of these women showed an almost complete lack of the hormone. Also the prolactin titer in the blood stream was low.

The genital organs, as determined by inspection of the external genitalia, vagina, and cervix as well as by bimanual palpation, were entirely normal. In addition, no constitutional disease or other endocrine imbalance was encountered. Such causes of bleeding as abortion, polypi, myomata, endometritis, and disease of the adnexa were carefully ruled out.

The curettage material showed wide variation in the thickness of the mucosa and the size of the various pieces of endometrium. The material, prepared by fixation in alcohol for various stains showing possible infection and glycogen secretion. The stroma is shrunken and composed of many deeply basophilic spindle-shaped nuclei. The spiral arterioles vary somewhat, but usually are
dilated and engorged. Occasionally, but particularly in those who have bled for some time, there are thromboses of these vessels. In some cases, there is extravasation of the blood elements into the stroma. The glands of the peripheral portions of the endome-trium are collapsed to form bizarre shapes, many of them suggesting 3, 4 and 5 pointed stars. The epithelium is obviously in the secretory or corpus luteum phase, as nuclei of the cells are discrete and located at the base of the cells, while the cytoplasm is clear, though low and irregular in outline, suggesting prolonged activity. The Best's carmin stain further corroborates the secretory phase, as many of the epithelial cells contain granules of glycogen which stain bright red with this medium. Other glands may show little or no secretory activity. The authors feel that the impression gained by study of tissue from such a patient is that it is predominantly a secretory membrane. This should serve to distinguish it from hyperplasia which is just as markedly non-secretory, or proliferative in type.

The work of Bartelmez has shown that in normal menstruation the shedding of the spongiosa is a progressive phenomenon in the sense that there is focal shedding at a given time and that subsequently other foci bleed and shed in succession. The duration of the menstrual period may be considered to be dependent upon the rapidity with which the various local processes succeed one another. Considering these facts it would seem probable that in this type of menorrhagia we may be dealing with nothing more complicated than a very much prolonged menstrual period. This leads to
a consideration of the factors which might be responsible for such a physiological abnormality. As the corpus luteum is in the ascendancy during this phase of the cycle, Kaudi feels that the most logical explanation would seem to be connected with that body or remotely with the hypophysis. All the histological evidence seems to point toward a prolonged and weak corpus luteum effect. In 2 patients in whom they were able to examine the ovaries corpora lutea were found presenting evidence of degeneration in the form of fat droplets in many of the cells. There were substantial zones of lutein cells which had the appearance of being well preserved and probably actively secretory.

Because no definite biological test for progestin is yet devised, it is nearly impossible to demonstrate any alteration of this hormone in these patients.

According to Traut and Kuder, both history and histological findings point definitely to mal-deciduation of the endometrium with prolonged and exhaustive secretory activity in the glandular elements of those fragments of spongiosa which remain attached to basalis. The stroma becomes shrunken and most often, its cells have changed from large round nucleated forms to a spindle shape which is characteristic of the proliferative phase of the cycle.

"Irregular ripening"or irregular maturation of endometrium is the other pathological picture found by Traut and Kuder in cases of menorrhagia. This they say differs from hyperplasia (the Graafian follicle stage) and from irregular shedding (the corpus luteum stage) in that it represents a mixture of both proliferative and secretory
In a study of 100 patients with excess bleeding, their findings were mixed histological picture in 21. Hyperplasia in 68 and irregular shedding in 11 were the figures recorded.

Histological pictures in these 21 cases of "irregular ripening" showed an endometrium which in the periphery zones showed considerable areas which were definitely non-secretory and others which were just as definitely secretory. In 5 of these cases the greater portion of the endometrium was in the non-secretory phase with only scattered areas of secretory tissue. The other 16 cases showed a more patchy distribution as regards secretion and non-secretion.

In making these studies only the superficial layers of the endometrium were considered since they manifested more typically the cyclical changes.

In conclusion these investigators (Traut and Kuder) of Cornell feel that both blood loss and tissue change are linked to the same process and that each is in some degree an expression of the other. They describe 2 rather new syndrome association with excessive bleeding namely: "irregular shedding" in which patients fail to shed surface spongiosa of endometrium normally and "irregular ripening" in which a mixture of proliferative and secretory phases are seen. Thus, since in normal menstruation the shedding is a frag phenomena they suggest that with this type of menorrhagia it represents only a physiological abnormality as of a prolonged menstrual period.
Irregular shedding of the endometrium. a) Collapsed glands with low secretory epithelium; b) Partially necrotic stroma.

Irregular ripening of endometrium. Two areas contrasting proliferative and secretory activity.
Blood content of Hormones

Fluhmann, in examining the blood of women, has demonstrated that there is a definite variation in the amount of estrogen present at different times during the course of the normal cycle. The peak of estrogen content is invariably found in the mid-interval at a time roughly corresponding to ovulation and occasionally a second rise occurs just before or at the onset of menses.

Frank and Goldberger have found that in a normal menstruating women, a 40 cc blood sample will not contain a full mouse unit until 7 days before menstruation. It again decreases with the onset of menstruation. The urine cycle is characteristically alike. The normal monthly output is 1200-1500 mouse units. Studies on normal children show little estrogenous substance usually excreted before puberty.

On the other hand a very different picture was noted in a group of patients with functional uterine bleeding. In 7 of 10 patients with menorrhagia and in 3 of 5 women with hyperplasia endometrii there was a sharp rise in the estrogen content of the blood, which occurred with the onset of the bleeding and then gradually decreased with the cessation of the flow.

It would seem that this variation from the normal may be of significance as a factor contributing to abnormal uterine hemorrhage.

Frank found that excessive bleeding as rule bespeaks overfunction of the ovaries because almost without exception, these bleeding cases show a markedly excessive excretion of estrogenic substance in the urine although the amount recoverable from the circulating
blood may actually be diminished.

While most patients show high estrin blood content because of estrin producing follicular cysts some patients show an entirely different picture.

Traut and Kuder did estrin determinates on the blood of a series of functional bleeding patients and found 4 of these women showed an almost complete lack of the hormone also the prolan titer in the blood stream was low.

Primary ovarian failure (an inherent lack of ovarian function independent of influence from other internal secreting glands) is encountered in about 15% of young women suffering of uterine bleeding. These patients are usually but not invariably underweight and are extremely feminine in appearance and demeanor.

In nearly 20% of the women suffering from functional uterine bleeding, Fluhmann and Smith recovered an excess of pituitary follicular stimulating hormone from the blood or urine. This suggests a compensatory hyperfunction of the pituitary gland in cases of inherent ovarian disability whether in young or menopausal women.

Thyroid derangements, either hypo or hyperhormone production may be responsible for abnormal uterine bleeding.
Causes

Uterine bleeding of endocrine origin may occur at any age between puberty and well-established menopause but it most frequently encountered at beginning and the decline of menstruation while the secondary phase of ovarian cycle luteinization, it most likely to be defective or absent.

Since the bleeding occurs at the time of normal menstruation and as a continuation of the normal function, some discussion of the causes of menstrual bleeding must be given for the possible relation they hold to the excess hemorrhage factor.

As a result of experiments on immature, mature and castrated monkeys (since certain monkeys have menstrual cycle comparable to that of human female). Allen, Maddix and Engle demonstrated the role of anterior pituitary hormones in products of normal menstruation and pathological bleeding in those animals. Similar work on the human has been done by Kaufmann. The following conclusions can be drawn from the work of these men.

1. A uterus subjected to the action of oestrin, bleeds when deprived of this hormone. The oestrin influence need not necessarily be removed completely but merely reduced.

2. Withdrawal from uterus of a corporeal luteal hormonal influence also causes bleeding.

3. Hemorrhage likewise results of the amount of a mixture of oestrin and progesterin stimulates the uterus is diminished.

Two different lines of thought have thus risen on the problem of the cause of normal menstruation. The first believes that it comes about as a result of the premenstrual withdrawal or demunition in amount of the follicular and corpus luteum hormones in circulation. The second postulates that the normal cyclical hemorrhage depends
merely on the premenstrual fall in the blood--oestrin curve and bears no relation to the amount of progestrin in circulation.

It seems almost impossible to entirely exclude the corpus luteum as a most important factor in menstruation since it has been shown that the occurrence of bleeding which follows a fall in blood oestrin level can be inhibited by progestin adminstration.

Other investments along same line include the demonstration of Chamoto and also Merange and Israel that menstruation can to some extent be delayed in its onset by administration of oestrin to normal women and again the work of Hesauyled Smith and Engle who showed that the corpus luteum hormone can inhibit onset menstrual flow in monkeys.

Whether the corpus luteum be involved or not the cyclic fall in the blood content of ovarian pituitary hormones is almost certainly the result of an automatic and reversible interaction which seem to exist between the pituitary and ovary.

Mozer and Rotz believe that the two ovarian hormones normally act upon endometrium in succession, first oestrin and then progestin, with rhythm and precision until corpus luteum regresses and progestin influence is withdrawn from endometrium resulting in the dismantling of menstruation.

The life and function of corpus luteum as well as those of its predecessor, the Graafian follicle, depends upon stimulation from anterior pituitrin where gonodatropic activity is apparently also cyclic and is synchronous with that of the ovary. The authors here attempt to show that the endocrinopathic uterine bleeding
is due to a break in the normal cycle, namely, the prolonged though not necessarily excessive production of follicular hormone estrin and absence of the balancing and controlling influence of luteal hormone progestin.

a. Endometrial hyperplasia

The etiological relationship between endometrial hyperplasia usually present in functional bleeding and follicle cystosis with defective luteinization or a total absence thereof was first suggested by Schroeder in 1919.

K. Tietze describes the findings of large cystic granulosa-bearing follicles in ovaries which produced excess estrin in the systems. He says "the result of this is a hyperplasia of endometrium, myometrium and mucus membrane of tubes. As a source of hemorrhage, the hyperplastic endometrium is of greatest importance.

Witherspoon and Collins of Tulane University further substantiate this idea for they say the idiopathic uterine bleeding results from a hyperplastic condition of uterine mucosa, hyperplasia of endometrium. It is no longer an hypothesis that this histopathologic change of endometrium is dependent upon ovarian dysfunction.

Endometrial hyperplasia is certainly the result of abnormal and persistent ovarian follicular hormone stimulation in the absence of any corpora lutea influence with a possible anterior hypophyseal action in the background. This ovarian hormone dysfunction in turn results from the presence and persistence of the multiple follicle cysts in ovaries.

According to E Murray Blair, one of the recognized authorities
on the causative factor of bleeding, states that in order to understand the significance of this condition of hyperplasia in functional menorrhagia, three things are necessary:

1. Picture of physiology of normal menstruation.
2. Picture of physiology of ovarian hormone products
3. Picture of pathological anovulatory cycle which is productive of endometrial hyperplasia.

![Diagram of normal menstruation cycle with ovulation, follicular ripening, and menstrual phases.]

The picture of physiology of normal menstruation shows a 28 day menstrual cycle. It is divided into quarters of seven days each. The cycle begins with a period of menstruation of five days. Following that a period of follicular ripening of 9 days. In this period a follicle proliferates, approaches the periphery of the ovary, protrudes beyond periphery and finally bursts, extruding its egg in the phenomenon of ovulation. Ovulation then usually takes place some 12 to 10 days, then degenerates and disappears, whereupon menstruation occurs.

The picture of physiology of ovarian hormone products represents the ovarian hormones produced during such a cycle. During the follicle ripening period, the follicle or oestrogenic hormone is
formed in the follicle. Following ovulation the hormone progestin is formed in the corpus luteum. The corpus luteum with its hormone persists for some 10-12 days then degenerates. Menstruation follows. Thus Blair says "there are only 2 ovarian hormones, oestrin formed before ovulation and progestin after ovulation". It is known, however, that some oestrogenic hormone is found in corpus luteum together with progestin.

The last picture represents the pathological cycle of hemorrhage.

In hyperplasia of endometrium there is one significance and practically constant finding—the absence of corpus luteum, hence no progestin and no secretory stage. There is however, a hyperplasia or overgrowth of the endometrium caused by an apparent over-production of the follicular estrogenic hormone. It might then be deduced that ovulation has not taken place in these cases but that instead the follicle is formed and continues to produce its hormone without subsequent follicle rupture, hence without subsequent corpus luteum and progestin formation.

The chief ovarian change is the absence of corpus luteum but another extremely common if not invariable accompaniment is the presence of one or more large follicular cysts. It is the content of these cysts carrying as they do quantities of oestrogenic hormone which stimulate the normal endometrium beyond its normal interval stage to the hyperplastic stage. Endometrial hyperplasia is then an overgrowth of the normal endometrium because of an overbundance of oestrin. Most hyperplastic endometria bleed quite profusely, but some exception have been noted.
It is probable that the reason ovulation did not take place was because the follicle was unable to rupture the surface of the ovary and so to rupture the surface of the ovary and so extrude the ovum. Later, follicles formed in subsequent months may meet the same fate, and so multiple follicular cysts may arise, each continuing to discharge its follicular or oestrogenic hormone into the circulation, and causing an overgrowth of its follicular phase. It is this overgrowth which is called "endometrial hyperplasia."

As Dr. Blair says "there are doubtless many causes for failure of the follicle to rupture". As women become older, the cortex of the ovary becomes firmer, and of a denser consistency. Of equal importance is the reaction of the ovary to infections from any cause, with its resultant, increased cortical density, exudate and adhesions. It has been recognized for many years that salpingitis cannot be spoken of as an isolated entity. Almost invariably the ovary also is involved in the process. Frankel also points out that infection may will play an important part in the formation of hyperoestrinism with resultant hyperplasia and bleeding. In support of this theory, it has been noted in Charity Hospital, New Orleans that practically all cases of hyperplasia is seldom seen in colored races without the associated chronic adnexal disease. It is also to be remembered that hyperplasia is seldom seen in the lower animals which are relatively immune to various infections, especially G.C.

The source and cause of the bleeding in endometrium hyperplasia are still unsettled problems. The degree of the hyperplasia does
not always determine the amount or character of the bleeding since Novak has found similar endometrial changes in women with amenorrhea.

Burch and Philp also believe that while hyperplasia is in part responsible for the hemorrhage, there are other as yet undetermined factors. The authors say "the changes in the endometrium are the result of an excessive proliferative production resulting from abnormal estrogenous stimulation." The bleeding of hyperplasia endometrium is due in some instance to factors other than hyperplasia as some cases of hyperplasia without bleeding have been noted.

Other observers consider small scattered area of necrobiosis, with localized thrombosis as the source of the hemorrhage. In apposition to this theory, Harman suggests an active bleeding factor originated in the anterior lobe, while Novak suggests a possible biological factor which increases the permeability of the uterine vessels. He does not believe the massive hemorrhages occasionally seen in this condition can be accounted for by the small necrotic areas in the endometrium.

Burch after vast experiments says that endometrium hyperplasia is only an overgrown and abnormal developed interest type of endometrium from which pathological bleeding results. He also believes bleeding can result from a type which cannot be differentiated from the normal. There is nothing in the histologic picture of these endometria to suggest an especially marked tendency to hemorrhage. Occasional areas of degeneration are found which in-
is now ample evidence that such "anovulatory menstration occurs in women. The diagnosis here depends of the demonstration of an endometrium in the estrogen phase", just before or during a period of bleeding. Four such cases have been demonstrated by the author. The amount of blood loss is generally within normal limits, however, such cases of excess bleeding have been noted.

c. Irregular ripening and shedding of endometrium

Traut and Kuder attempt to explain the cause of bleeding as due to the picture of irregular endometrium ripening and shedding. They refer to the work of Bartelm who has shown that in normal menstration the shedding of the spongiosa is a progressive phenomenon in the sense that there so focal shedding at a given time and that subsequently other foci bleed and shed in succession. Hence, the duration of the menstrual period may be considered to be dependent upon the rapidity with which the various local processes succeed one another. They suggest that in the light of these facts that in this type of menorrhagia, we may be dealing with nothing more complicated than a very much prolonged menstrual period. However, they do not in this way explain the fact that the hemorrhage is not only prolonged but often exceeds the normal in amount.

d. Progestin

It will be remembered here that one of the facts concerned with the cause of bleeding in normal menstration was demonstrated by the experimental work of such men as Allen, Moddux, Engle and Kaufmann to be the withdrawal from uterus of corporal luteal hormone influence.
There must also be some proportional relationship between amounts of estrin and progestin to maintain normal balance. Earlier investigation were at loss to explain the presence of occasional corpora lutea in presence of excess bleeding. However, further investigation disclosed that massive follicular cysts producing excessive amounts of estrin were also present in the same picture. Reasoning thus explained that the small amount of progestin was much out of proportion to the amount of estrin, hence estrin effect of hyperplasia predominated with the present finding that most patients having excessive bleeding as complaint are usually sterile, and also experimental investigation on animals, it is believed now that ovulation has not occurred hence no corpus luteum--no progestin--and only an unopposed action of estrin and hyperplasia are present. Thus, it is seen that lack of progestin, while only the result of other causative factors, is usually one of the most important, if not the most important, immediate causative factor on bleeding.

Progestin lack in puberty bleeding, arises probably not from follicular cyst formation or an anovulatory condition but as Kane suggests, it is probably due to the fact that the pituitary glands has begun to function before the ovaries have become capable of forming corpora lutea. The follicles are stimulated by prolan A, estrin is formed and the endometrium becomes vascularized, but there is no progestin to stop the process. This condition is not due to an excess of estrin as the blood test is usually negative; it is the lack of progestin by which the action of estrin might be checked.

G. W. Corner after extensive experiments on monkeys makes the
statement "corpus luteum hormone, progestin, has the definite property of inhibiting menstrual flow in monkeys. This also agrees with the findings of Smith and Engle who showed that experimentally induced menstrual like bleeding could be inhibited by doses of progestin.

Pratt of Henry Ford Hospital has made the observation that removal of corpus luteum during the latter half of the intermenstrual period is followed by bleeding.

All this experimental work would suggest progestin lacks as the definite causative factor, however, it must be remembered that it is only the final step in a series, and any successful treatment must be directed at the series of causative factors.
Diagnosis

While the diagnosis of menorrhagia may be made by the presence of excess or prolonged hemorrhage at the time of normal menstruation, a diagnosis of the primary condition acting on the causative factor is much more difficult.

An examination of the pituitary should be done. Crossen follows a routine of x-ray examination of the sella turcica, sugar tolerance tests and examination of the visual fields.

Hormone tests carried out in series is suggested by Frank in his extensive work on this type of functional bleeding as an important diagnostic measure.

This requires a laboratory suitably equipped and the finding must be properly interpreted to act as a guide in treatment. This interpretation portion is much more difficult than it at first would appear.

Crossen further states that if the facilities for the methods of direct investigation are not within reach, a test of treatment may be employed. This consists in giving the anterior pituitary-like hormones, obtained from urine (antuitrin-S, follutain, antoplupin, A.P.L.) in combination with some extract of the anterior pituitary (gynatrin, prephysin or the growth hormone) containing pituitary-A. The first group therefore, have a preponderance of the hormone resembling prolan A and secondary group a preponderance of prolan B. Since it is known that prolan B aids corpus luteum formation and the normal starting and stopping of the flow, while prolan A aids the normal growth of follicle and normal ovulation, the results
of their effects might be suggestive of the causative factors.

Curettage is an important diagnostic measure in that it aids in ruling out infection or malignancy which otherwise might be missed. The preferable time for the curettage is just before the flow starts. At that time, the curettings are most likely to give information which would be decisive between hyperplasia (indicating non-ovulation) bleeding and excessive menstrual flow.

Dr. Sage has given an excellent clinical picture of the young woman with pituitary failure as contrasted with the young woman with ovarian failure that will serve as excellent means of designating the site of pathology.

Pituitary Failure

1. Menstrual irregularity and if married, sterility.
2. Inclined to be obese and will have low metabolic rates.
3. Prolan is not demonstrable in their urine and estrin is lower than normal or not demonstrable.

Ovarian Failure

1. Menstrual irregularity and sterility.
2. Usual normal weight and normal metabolic rates.
3. Prolan is always normal or in excess, depending on the degree of ovarian failure, values for estrin vary greatly but is not absent entirely, unless there is complete ovarian failure.
4. These women often have vasomotor disturbances such as hot flashes during periods of amenorrhea; soreness of breasts, pelvic pain with nausea and vomiting; a migrainous type of headache, aching in lower part of back and thighs, nervous irritability, skin manifestations such as acne, urticaria, or angioneurotic edema may antedate or accompany menstruation.
Crossen and Crossen have formulated one of the best complete charts comparing the clinical pictures of the possible glands at fault in the endocrine dysfunction group of menorrhagia to be used as a diagnostic means.

**Endocrine dysfunction**

**Ovarian**

**Hyperfunction**
Normal vitality, early sexual maturity, libido increased, fertile. Curettage at proper time shows menstruating endometrium.

**Hypofunction**
Weak and atonic, poor secondary sexual characteristics, libido diminished, sterile. Curettage at proper time shows non-ovulatory hyperplasia of endometrium.

**Tumor**
(ovarian)
In early life—precocious menstruation and precocious sexual development, in regard to breasts, pubic hair, etc. After menopause—return of menstruation and other evidences of ovarian activity.

**Pituitary**

**Hypoantuitism**
Statural overdevelopment, gigantism. Tall, well muscled, no excess fat. Sexual overdevelopment (feminine).

**Thyroid**

**Hypothyroidism**
Associated with hypofunction of ovaries and non-ovulatory bleeding.

**Hyperthyroidism**
Associated with mixture of hyperthyroid symptoms and hyperfunction of ovaries.
The wide age distribution of functional bleeding makes necessary a variation in the objectives of its treatment. The ideal therapeutic method would have for its result cessation of the excessive hemorrhage and preservation of the normal menstrual and procreative function. However, in the older class of patients as regards procreative function that is in the women past 41 or 42 years of age, satisfactory result would include the return of normal periods or amenorrhea without severe menopausal symptoms. Recorded results from the use of various type of treatment show that none of these even approached the ideal—however, each investigator seems inclined to believe that the product he has worked with has most nearly approached this. Keene and Payne make the statement that "only too often methods are employed with the control of bleeding as the only objective and with entire disregard of the disastrous sequelae which may accompany the destruction of ovarian or reproductive function."

However, in a few cases where severe emaciation and anemia have resulted from the prolonged hemorrhage, immediate transfusions, and treatment of circulatory collapse are necessary. Curettage here is valuable therapy in that it results in temporary immediate cessation of the bleeding and also offers time for further treatment as well as a diagnostic means.

Proof that the ideal treatment of functional bleeding has not been found is seen by the large number of therapeutic procedures which have been and are still being introduced. These
Methods may be divided into seven groups:

1. Hygienic measures
2. Uterine stimulants
3. Means to decrease the coagulation of the blood or to decrease the permeability of the vessels.
4. Endocrine therapy
5. Removal or destruction of the endometrium
6. Roentgen or radium therapy
7. Surgical procedures upon the ovaries or uterus.
   a. Hygienic measures

Hygienic measures are of value when used in conjunction with other appropriate medical and glandular therapy. Keene and Payne feel that constitutional defects often are attended by disturbances in endocrine function which are expressed by abnormal uterine bleeding. Lawrence emphasizes the importance of dietary deficiency, particularly improper nitrogen balance, correction of which may result in the return of normal menstruation. In addition to this as most investigators know, irregular bleeding may accompany severe secondary anemia and often responds quickly to correction of the anemic state. Again, focal infection may be a factor in reducing the constitutional stability of the individual with an increased tendency to abnormal uterine bleeding. Alterations in menstruation with either the development of abnormal hemorrhage or a return to normal periods is occasionally seen following a change in vacation, climate or environment.

Crossen states that he puts his patients on a general regimen to control the bleeding and make up for the blood loss. This
consists of blood building foods as liver, spinach, carrots, prunes, peaches, raisins and apricots. Iron is given in its various combinations such as iron-ammonium citrate, 10-20 grains three times daily or liver and iron preparations as lextron or jeculin.

b. Uterine stimulants

Various uterine stimulants have been recommended in abnormal uterine bleeding under the assumption that it is due to faulty contractibility of the uterine muscle incident to malposition, chronic subinvolution, or inherently poor muscle tone; Diasio reports excellent results from the use of ergotamine tartrate. Extracts of hydrastis have been used as uterine stimulants for years according to Keene. The most active is hydrastinine hydrochloride which, according to Cushen, stimulates powerful uterine contractions. Cotarmine chloride (stypticine) has a similar action, but according to Cushny is inferior to hydrastinine. Favorable results have been reported in an article by Martzloff from the use of pituitrin during active bleeding, and VanderHoeven found that adrenalin chloride checked the bleeding in a small number of patients. Intravaginal ultraviolet therapy is recommended by Handiler who combines this with the administration of calcium and the anterior pituitary-like hormone. It is the belief of Keene and Payne that the condition of the uterine musculature has little or nothing to do with abnormal uterine bleeding except in the case of the subinvolution following pregnancy.

c. Blood coagulants and Endothelial stimulants

Substances which affect the coagulability of the blood or the
permeability of the capillary walls have been added recently to the list of therapeutic agents in functional bleeding. Moccasin venom was introduced by Peck and Goldberger in 1933. It has been used with good results in 17 to 20 cases of excessive bleeding.

The control of hemorrhage probably results by means of action of venom on uterine capillaries Peck and Goldberger believe, making these vessels more resistant to hemorrhage.

Adequate dosage based on clinical symptoms must be determined for each patient.

The venom was used in 1:3000 diluted with sterile saline containing 1:10,000 merthiolate. All injections were given subcutaneous beginning with .5 cc and increasing to 1 cc on 3rd injection. The time interval depends on severity of bleeding. It is considered advisable to give as much venom as possible the first 10 days because at about that time the majority of patients developed a sensitivity to venom while necessitated a decrease in amount until desensitization occurred. In severe cases 1 cc was given once and even twice one day until bleeding ceased and then reduced 2-31 weeks. If following menstrual period was nearly normal, 2-3 doses one week were given for at least three following periods.

Of 47 cases collected from literature, bleeding was controlled in 42 (90%). Recurrences of bleeding again necessitated 1 cc initial doses but it was noted that the course of injection was shorter than on the original treatment.

Although older patients often respond, Watkins has pointed out in his article that the results in adolescence are always more
Cevitamic acid, which is the active principle of vitamin "C", has been used in German clinics for some time. Fifty milligrams of cevitamic acid approximately corresponds to the active vitamin "C" in 100 cc of fresh orange juice. Marked deficiency in vitamin "C" results in scurvy with its hemorrhagic manifestations. According to Albrecht, cevitamic acid prevents dissolution of the endothelial cells, thus decreasing the permeability of the capillary walls. Schroeder found a prolongation of the coagulation time in vitamin "C" deficiency. It seems that cevitamic acid acts upon the blood and blood vessels. The technique of administration consists of the daily intramuscular or intravenous injection of 50 mg. of cevitamic acid in an isotonic saline solution. According to the reports, this usually checks profuse uterine bleeding within four to six days. Junghaus reported 35 patients with preclimacteric bleeding, of whom 33 were relieved. A total of 46 cases was collected from the literature with 43 (93 per cent) satisfactory results. While age does not seem to influence the results, the majority of the patients in this series were in the climacteric era.

Intravenous injections of Congo red have been used for the control of venous bleeding of various types, including uterine hemorrhage. Roasak found that these injections resulted in an increase in thrombocytes and a decrease in the coagulation time of the blood. Studies on the action mechanism of Congo red revealed that Congo red does accelerate the coagulation of blood by increasing the number of thrombocytes compressing the capillary lumen by ad-
herence of color granules to the perithelial cells and finally by the partial destruction of erythrocytes and resulting formation of hemosiderin in the cells of the reticular-endothelial systems. Graves and Kickham recently reported a series of urologic patients in whom Congo red was effective in controlling acute bleeding in the presence of normal blood coagulability. The recommended dose is 5 to 10 cc of the sterile isotonic solution administered intravenously. A single injection often checks the bleeding or several injections may be necessary at two to three day interval. Of 30 patients with functional bleeding who have been reported, 21 (70 per cent) responded to the injections, 5 (17 per cent) were partially relieved, and 4 (13 per cent) were not benefited. The drug seems to be effective even in the absence of blood dyscrasia but recurrences of the bleeding are common. However, in his reports on 36 patients, Nikolajew and Gurewitsch feel that the action of the dye is active only in menorrhagia of an inflammatory nature.

d. Endocrine therapy

**Estrin** Since functional bleeding is caused by abnormal endocrine therapy activity, practically all of glandular products have been given a trial in the treatment. Drips in 1934 reported improvement in 71% of 94 patients from the use of estrin (sistomenin). Later, Siebbe reported that half of his patients responded to estrin therapy. Estrin in large doses may delay uterine bleeding temporarily but its curative value is doubted by all gynecological endocrinologist according to authors Keene and Payne.

S. Zuchermann found that estrin when administered in adequate
amounts throughout cycle delays onset of the next period. Uterine bleeding will not occur during the course of daily injections of adequate amounts of esterin in either normal or castrated subjects.

It may occur if daily dosage is of threshold or subthreshold value or if absorption hormone is imperfect. Zuchermann concludes that such a means of delaying the period in only controlling the hemorrhage in as much as it delays its onset.

Corner after extensive experimental work makes the conclusion that simply maintaining the estrin level by injection of progynon B or crude follicular estrin is not sufficient to prevent the onset of menstruation. It is well known that continuous administration of estrin decreases the production of the gonado-stimulating hormone by the hypophysis and is therefore probable that during the later stages of the course of estrin treatment that deep-seated disturbances of the pituitary-ovarian balance may result.

**Insulin** Klaften reported 48 cases of functional bleeding, many of the patients with diabetic backgrounds, in 32 of whom bleeding ceased following the use of insulin and high carbohydrate feeding. This treatment normalized the flow in some cases of profuse bleeding. The period of bleeding was shortened in many cases but intensity hemorrhage was not affected. In 12 cases of juvenile hemorrhage matropathy, the results were likewise favorable but in preclimacteric bleeding no good results were achieved. He points out however that recurrences are frequent and more likely to occur as the age of the patients advances.
Corpus Luteum  Theoretically corpus luteum extract should be of value in the treatment of functional bleeding, but Keene further comments that until very recently, potent extracts have not been available for clinical use. It is now supplied in ampules which vary in content from 1/25 to one rabbit unit.

In mature monkeys, uterine hemorrhage occurs after deprivation of estrin supply. Engle and Smith found that this bleeding can be prevented by the administration of progestin. This prevention usually lasts 10-12 days, sometimes 28 days. Bleeding occurs 4-5 days after the cessation of progestin.

This bleeding following progestin cessation will occur even though estrin administration is begun at once and continued until bleeding commences. Evidence from other investigators with the human cycle indicate that in humans also, menstruation results from cessation in secretion of corpus luteum and occurs in the presence of high estrin content of the blood.

Corner is quite in agreement with these findings for he concludes from his experiments that "the corpus luteum hormone, progestin, has the definite property of inhibiting bleeding.

Thus, it can be seen that since hyperplasia and the accompanying hemorrhage are brought about by an unopposed action of oestrin, the treatment necessitates either the administration of the missing corpus luteum hormone or the production of an active corpus luteum in ovary. The former treatment may be referred to as a "replacement" or "substitutive therapy" while the latter is generally termed the stimulating therapy.
Bishop, Cook and Hampson believe that progestin should be given in combination with the anterior pituitary extract. The anterior pituitary factor should be administered continuously by injection of up to 500 rat units 3 times a week in a course of 2 months and if necessary may be repeated after a two month period. In the premenstrual phase and during the actual bleeding, anterior pituitary extract should be given daily, together with one rabbit unit of progestin.

Kauffmann was able to produce, a premenstrual endometrium in a castrated women with 50,000 rat units of estrogenic substance followed by 35 rabbit units of proluton.

Keene and Paye emphasizes that the probability of such endometrial changes follows the small doses of progestin often now used is held questionable.

Wilson and Elden suggest that with the ovaries in situ possibly a certain amount of progesteron is produced in the follicles undergoing atresia and this may be supplemented by its hypodermic administration. These authors controlled abnormal uterine bleeding in 5 patients with hyperplasia with the total doses of progesterone varying from 2/25 up to 15/25 rabbit units. The permanency of the results is open to question since the therapy is substitutional and recurrences of bleeding will probably follow cessation of the injections. Any permanent relief would therefore require continued accompanying hormonal administration.

Thyroid Functional bleeding is often associated with various degrees of hypothyroidism. Plass points out the value of thyroid
therapy in adolescent hemorrhage even in the absence of definite evidence of deficient thyroid function. In a study of 59 patients with myxedema, Gardener, Hill and Smith found menorrhagia to be a common complaint. The exact effect of thyroid is not known but it seems to aid in regulating the rhythm of gynecologic endocrine cycle. It is usually administered in conjunction with other endocrine products, particularly the urine or placenta prolact extract.

According to Kane, the thyroid, while not primarily associated with sexual function, to some degree affects the action of all the other endocrine glands. In cases such as those under discussion, it has been found that even though the basal metabolic rate may be normal, small amounts of dessicated thyroid are usually beneficial. Dosage of 1/2 grain of dessicated thyroid 3 times a day seems sufficient to augment the effects of the special hormone being used.

A group of patients with menorrhagia and low Basal metabolic rate were treated by Haines and Mussy with carefully regulated oral doses of dessicated thyroid. No other form of treatment was used while these experiments were being conducted.

Definite improvement in menstrual flow was obtained in 73% of cases of menorrhagia as well as about 75% of these reported improvement in their general health after elevation of basal metabolic rate to within normal limits.

It is the opinion of R. G. Hoskins that menorrhagia in young girls is often associated with hypothyroid condition. The stimulating
property of thyroid hormone can be utilized in case of variety of deficiencies involving other glands. There is direct evidence that some glands are stimulated by this agent, and presumptive evidence this is true of others.

The initial dosage of thyroid is governed by the basal metabolic rate and the clinical status of the patient, varying from .5 to 1 grain per day. Every two weeks the dose is increased .5 grain a day until patient's level of tolerance is reached, as evidenced by her nervous reaction, tachycardia, dyspnea or loss of weight. It is continued for at least 3 months before it is judged ineffective and if satisfactory results occur, it should be administered even longer.

Urine prolan (Antuitrin-S, Follutein, Antophysin, A.P.L.) Kane emphasizes the fact that the object of treatment of functional bleeding during puberty and maturity is production of progestin. The bleeding is caused by the excessive action of estrin and may be controlled only by providing sufficient antagonism to that hormone. Commercially available progestin would be only substitutive. Almost certainly would it control the hemorrhage but it would be necessary to repeat treatment with each period of bleeding.

It is thought that by stimulating luteinization of Graafian follicle and corpus luteum through administration of anterior pituitary hormone, it is possible to produce sufficient progestin to stop most cases of functional uterine bleeding.

Available preparation of prolan contain the follicle stimulating estrin producing hormone as well as the luteinizing principle, but
prolan B is present in quantities sufficient to dominate the action.

The amount of prolan obtainable from pituitary gland tissue is far to small for it to be easily available therapeutically. Large amounts are, however, to be found in urine of pregnant women and this is the source of the commercial preparations.

As H. F. Kane points, while standardized commercial preparations are available it is more economical to employ the whole urine from pregnant women. Urine from patients known to be free from syphilis and tuberculosis may be sterilized in Berkefeld filter and given intramuscularly in 20 cc doses. As prolan content rises rapidly during the first 5 months of pregnancy and drops as quickly, the largest amount of prolan is present at the end of 5 months. These preparations are sold commercially as A.P.L. substances, Follutein, Antuitrin-S, Antophysin.

Estrin, however, is also present at 5 months, the amount almost equals that of prolan. To secure the maximum amount of prolan with the least amount of estrin, urine from patients in the 2-3 month is used.

In 1931 Novak and Hurd reported cessation of bleeding in 44 of 51 patients who were treated by injections of urine prolan extract. The exact action of this substance is not known. Geist and later Hamblen and Ross have proved that it does not cause luteinization of persistent ovarian follicles. Hamblen has shown recently that endometrial hyperplasia is unaffected by large doses of prolan.

Novak suggests "that the effect is exerted upon some unknown
bleeding factor", which seems to be "bound up with a disturbance in the balance between the two anterior pituitary hormones".

Smith and Rock suggest a direct action upon the hypophyseal secretion. They believe that in view of the fact that immediate cessation of the bleeding at times follows the injection, one must assume that the effect is produced substitutionally and is not due to a modification of ovarian or pituitary function.

Bishop, Cook and Hampson indicate the same idea in their writings. Because the flow in some cases of dysfunctional bleeding ceased promptly after the injections of pregnancy urine extract, before active luteinization or progestin formation could take place, and because even several days after injections were started and the flow stopped, no evidence of progestin effect could be found in the endometrium. They believe that some other mechanism than luteinization is responsible. They suggest that the immediate effect may be that of pregnancy urine on Novak's "bleeding factor".

Some men as Tachezy and Worchowsky claim good results by using pregnancy urine in the form of retention enema. This is a commercially inexpensive method of administration. However, from a therapeutic aspect it is considered to be too crude and disagreeable for the patient. A cleansing enema is given first, then 100 cc of urine as often as once or twice a day. The author believes that good results are due to the fact that it is not a pure hormonal preparation and is rapidly absorbed. He points out that Siegert likewise expressed the opinion that "incompletely purified preparations are more effective. It is possible that the accomp-
anying substances facilitate absorption.

Witherspoon reports 12 cases with menorrhagia were given a series of daily injections of 250 rat units of anterior lobe lut-
einizizing hormone in the form follutein. In 8 cases the bleeding was successfully checked. One patient had 11 normal menstrual periods following treatment. Another patient became pregnant after restoration of the normal menstrual cycle.

Gabrielanz, Collip in Canada and Gallatine in Chicago are using water soluble extract of prolan. They inject 2 cc sub-
cutaneously on alternate days until bleeding ceases. These men feel it acts purely as a luteinizing hormone.

Henderson of Toronto reports treating 39 cases, presumably due to endocrine disbalance by A.P.L. like hormone. Of these 31 were relieved of menorrhagia and 25 had a complete return to normal menstruation.

His conclusions were:

1. A.P.L. hormone is a valuable therapeutic agent in menorrhagia due to endocrine disfunction.

2. Moderate diffuse enlargement of the uterus is frequently encountered in functional bleeding but is not a counter-indication to hormone therapy.

3. Harmful effects of A.P.L. are considered unlikely and are outweighed by the excellent results.

4. Improvement of the patients general sense of well-being is noted and frequent relief of dizziness, when associated with menorrhagia is observed.

**Anterior Pituitary extract** The anterior pituitary may be adminis-
tered in several forms. Prior to the introduction of more potent urine extract, sterile of early pregnancy was injected intramuscular-
ly with good results as to bleeding but with frequent severe local reactions.

Recent investigation by Evans, Leonard and Collip working on hypophysectomized rats, have shown a dissimilarity of action between the hormone found in pregnancy urine and the sex stimulating hormone contained in anterior pituitary extract or whole gland transplants. In the hypophysectomized rat, the pregnancy urine hormone gives rise only to thecal cell luteinization around atretic follicles, while the latter causes follicular activation and maturation and the formation of fresh corpora lutea. Evans, however, drew attention to the synergistic action of these two hormones. He showed that the effect on experimental ovaries is much greater than when either is administered alone, and is greater than the additive effect of the two combined. This synergism of the pregnancy urine hormone is demonstrable with either the gonad stimulating principle of the anterior lobe or with the pituitary growth hormone. The factor responsible for this synergistic action has not yet been identified with any of the known pituitary hormones.

Evans theorizes on the existence of this factor in the pituitary gland in a prehormonal state. With the action of the pregnancy urine upon it, the prehormonal factor is converted into the anterior lobe sex stimulating principle, which, upon its release causes the typical Aschheim-Zondek reaction in the ovaries, the production of ripe and ruptured follicles, and fresh corpora lutea. If this hypothesis be true, the hormone of pregnancy urine is a pituitary stimulating rather than an ovarian stimulating principle.
In view of the greater ovarian response as just described by the administration of anterior pituitary extract in combination with the hormone of pregnancy urine over the latter alone, this method of therapy was used in the treatment of functional uterine bleeding.

The technique of the treatment consists in the daily administration to bleeding patients of 1 cc of follutein alone or in combination with 2 cc of anterior pituitary growth hormone. These injections are given intramuscularly until bleeding stops. Assuming this cessation of the flow to be the end of menstrual period, no further hormonal therapy is given until the onset of next period and carried on till it ceases. A third period of treatment is also carried out but the next or 4th period is missed with hope that menstrual rhythm has been re-established. Three months treatment was in the hands of the authors Witherspoon and Collins, usually sufficient; few, however, required more. About equal results were obtained whether follutein was used alone or in combination with growth hormone.

The actual conversion of the hyperplastic endometrium over into the secretory, premenstrual phase did not always occur, is readily seem by the rapid cessation of the flow, within 12-24 hours after the injection of the hormones. The smallness of the dose injected and the rapidity with which the bleeding stopped would tend to preclude the described change. The most likely explanation would seem to be that the hormonal effect is exerted upon some unknown bleeding factor, which possible is similar in nature and function
to the principle which controls the cessation of the normal flow.

Blood from pregnant women or blood serum has been found effective in 87% of 84 patients by Clauberg and by Witherspoon. A series of 32 cases of functional bleeding, 8 of which fit into the classification of menorrhagia were treated by Witherspoon, and in all these 8 cases he reports excellent subjective results with resumption of the normal periods lasting anywhere from 3 months in one case to 11 months in others. The technique employed included the withdrawal of 10 cc of venous blood from cubital vein of women in early months of pregnancy and injecting it immediately into the buttocks of patients. Ten cc was chosen arbitrarily as desired dosage. Witherspoon sums up his work by giving first advantages of this type of therapy, and later the disadvantages, which he says outweighs advantages.

Advantages are:

1. **Cheapness and convenience** since obstetrical and gynecology wards usually are adjacent.

2. **Normal ratio of ovarian and pituitary hormones** is present.

Disadvantages

1. **Patient objects** weekly injection of different patients blood even if the Wassermann is negative.

2. Painful local reaction occur in some cases.

3. **This treatment might circumvent** diagnostic curettage and biopsy, two procedures very necessary to rule out malignancy.

4. **Inconvenience of sterilizing necessary amount of blood** for clinical use as the stability of hormone is known to be temporary.

5. **No exact status of hormonal ratio** in pregnancy blood is known.
The prolan extract now available for clinical use are derived from the urine of pregnant women or from the placenta. Keene and Payne found in 483 collected cases, satisfactory results were obtained in 347 patients (71%), 35 (8%) have been partially relieved or have had recurrences and 101 (21%) have been unaffected.

Campbell reports largest single series of 78 cases in which placental extract was used and bleeding controlled in 72 or (91%). He, however, found prolan less effective in menorrhagia than in other bleeding disorders, while Smith and Rock in a latter report on a series of 56 cases found urine prolan to be most effective in menorrhagia.

The origin of urinary "Hebin"—as Burch termed the active principle in pregnancy urine has been ascribed to the anterior hypophysis. Recent work has cast some doubt on this origin because urinary hebin is ineffective in hypophysectomized animals and the amount of ovarian enlargement produced is proportional to the dose only to a certain point. After reaching this point no greater uterine enlargement results no matter how much is injected. Anterior hypophyseal hormone on the contrary, gives an ovarian enlargement which is proportional to the dose. The amount of ovarian enlargement when the two are given together is greater than the sum of their effects, which would suggest a specific activation of the anterior pituitary sex hormone by hebin. It should also be remembered that urinary hebin is similar in many respects to A.P.L. substance of the placenta.

Burch believes that since the prolonged bleeding in cases of
endometrial hyperplasia is the result of degeneration of endometrium, which in turn is a result of a deficiency of estrin and which in turn is a result of the diminished secretion of anterior lobe, it is apparent that any substance that activates that anterior lobe and starts the secretion again will in turn activate the ovary and check degeneration in the endometrium and when this is accomplished bleeding will stop.

While the main action of extract of pregnancy urine is directed on the anterior lobe, there is some immediate action on the endometrium as the bleeding is very frequently increased for a time during the course of injections.

According to Novak and Hurd, the two important hormonal principles Prolan A and Prolan B cannot as yet be readily separated. Though both are present in preparations used, the dominant action is that of the luteinizing hormone. This is to be expected when it is remembered that in early pregnancy the ovaries contain a large amount of lutein tissue, represented by the corpus luteum of pregnancy, and probably also by a considerable amount of theca lutein tissue. Furthermore, follicle activity is in abeyance at this stage.

Wiesner in explaining this dominantly luteinizing effect of prolan found that prolan A rapidly deteriorates soon losing its effect on standing. He also believes that the maximum effect of prolan A is reached long before that of B, so that the effect of their combined administration is that of Prolan B or luteinizing. Most preparations are therefore standardized for prolan B.
Keene and Payne report that their experience has been more satisfactory with placental extract than with urine extract, although the former is more likely to cause local or mild constitutional reactions.

They claim that their best results with prolan were obtained in the younger patients. Of these less than 20 years, 78% responded satisfactorily; 73% of 20-30 year group recovered and in 67% of those between 30-40 the bleeding was controlled. They rarely employed prolan therapy in patients after the age of 40 because they have found it is usually ineffective, at best being only of temporary benefit. Of 168 patients whose ages were given in various reports in literature, 74% of adolescents and 58% from 20-30 years of age were satisfactorily affected. In 30-40 group 72% were relieved and only half of those from 40-50 years.

The authors employ a slightly different technic in the administration of prolan. They inject 200 rat units per day until bleeding ceases or until 10 injections are given and then 100 units every 3rd day until bleeding stops.

**Mammary gland therapy** Thomas Cherry describes mammary gland therapy in menorrhagia. The basis of this treatment involves an explanation of breast-ovary endocrine interrelationship.

It has been known to both laity and medical profession for some time that the lactating mammary gland has an inhibitory influence on ovulation and menstration. Many lactating mothers who are not desirous of again becoming pregnant will continue nursing their infants for a prolonged period.
It has been shown experimentally that development of the mammary gland depends upon stimulation by estrin from the Graafian follicle. The action of progestin seems inert in this respect. During the state of pregnancy there is tremendous increase of estrin in the circulation which reaches its peak just before parturition. During the latter months of gestation, the mammary gland increases in all its elements when delivery takes place, there is a sudden drop in estrin content. This according to investigators, releases the inhibitory action upon the anterior pituitary hormone and the lactogenic hormone of anterior pituitary becomes active in stimulating alveoli in secretion of milk. The fact that during lactation period in the majority women, menstration does not take place, can be explained Cherry believes, by the low level of estrin in circulation, that is inhibited by some antagonistic hormonal action from lactating breast preventing maturation of Graafian follicle.

It is upon this basis that mammary gland extracts have been used successfully clinically in treatment of menorrhagia.

Experiments on rabbits given gonodatropic stimulating substances in combination with mammary extract, showed the ovaries in most instances to have completely absent corpora hemorrhagica and corpora lutea. Follicular development was present in the majority cases but in some there was an absence of this development.

Cherry reports a series of 50 patients at Columbia University who had menorrhagia of glandular origin were placed on mammary therapy. These included patients in child-bearing period of life, varying 23-49 years age. The cases were subdivided into severe
where bleeding seriously interfered with the duties of life and produced secondary anemias and moderate where blood loss incapacitated lesser degree. Estrin determination on these patients showed a definite increase.

In applying mammary therapy, Cherry discovered early that dessicated powder in form tablets or capsules had little effect. Therapy was thus confined to liquid preparation of dessicated powder administered both orally and intramuscularly. The other preparation was an extract from the raw lactating gland given intramuscularly.

With few exceptions all patients showed improvement in diminution of excessive flow. In severer forms anemia was such as require transfusion also in the treatment.

Cherry found that a more rapid response was obtained from raw lactating preparations than from dessicated powder preparations. The raw lactating product was more potent requiring much smaller dosage (1-2cc) in comparison to 5-10cc dose for the latter, thus rendering the administration much less difficult to the patient.

However, the application of mammary therapy must be a tentative one since individual response is difficult and serious damage to the follicle apparatus, producing complete ovarian inhibition may result from the excessive use.

Cronental describes treatment of uterine bleeding by stimulating the mammary glands with galvanic current. The author employed galvanic stimulation in 334 cases of menorrhagia and metorrhagia
and says he obtained improvement in 86% cases. The method includes application to the mammary gland with the exception of nipple, of flannel cushions saturated with 0.33% saturated potassium iodide over which lead plates are fixed and then connected to the cathode. The anode is a carbon electrode introduced to the vagina with non-insulated parts contacting the cotton tampon saturated with 1:1000 calcium chloride. Cronental has later improved on his methods by replacing the vaginal electrode with the abdominal plate electrode. He also intends to replace galvanic current by diathermy in future cases.

**Destruction or removal of endometrium** The present conception of causes underlying functional bleeding would seem to cast discredit upon curettage and other methods of removing the endometrium, however, many satisfactory results have been reported from the use of such measures.

Holzapfel advocates steam vaporization of the uterine cavity and reports excellent results in 111 patients, although 2 of them died. A small 2 way cannula is placed in the uterus and steam at a temperature of 125-30 degrees C. is applied for one minute. This is followed by a short rest and the procedure is applied 4-5 times at one sitting.

He warns that the vaginal walls must be well protected by gauze sponges and the escape of the steam must be unhampered.

A second method of endometrial destruction is the use of zinc chloride in solution or in pencil form. Vorster treated 100 cases with zinc pencil and obtained satisfactory results in all. He
states that a "moderately febrile reaction occasionally follows the treatment and a profuse discharge persists for some time."

Theilhaber recommends the intrauterine application of a diathermy pencil, with the indifferent electrode on the abdominal wall, a vulcanite uterine sound is heated until it causes blanching of the vaginal lining. It is then introduced into the uterine cavity and the current is applied for 15 seconds. One hundred and fifty eith young women were treated by this method with no untoward reaction and his results were reported as "satisfactory".

Curettage, in the experience of Traut and Kuder, with removal of the remaining endometrium has been sufficient to cause prompt cessation of bleeding in cases of menorrhagia due to irregular shedding of the endometrium. Most patients then resume the normal cycle.

Many of the above methods for endometrial removal are condemned by most authorities but curettage is still considered quite important in the diagnosis and treatment of functional bleeding. C. J. Miller was a firm advocate of curettage in adolescent bleeding.

Geist and Glassman reported 142 patients treated by curettage with satisfactory results in 52%, partially satisfactory in 12%, and no relief in 35%. Except in adolescents, they believe the initial therapeutic steps should be curettage but that a cure is unlikely in presence of endometrial hyperplasia. Martin's figures further confirm this idea. He found 64% recurrences in 94 patients with hyperplasia treated by curettage alone.

Keene and Payne report poor results with curettage with 50
recurrences in 2 months. In general, it would seem that curettage offers an excellent means of immediate stoppage of bleeding, thus, preventing secondary anemia and also allowing time for further diagnosis and treatment.

f. Irradiation

X-ray In the treatment of menopausal menorrhagia, organotherapy is of little value. The bleeding is due to an absence of corpora lutea or their inability to produce progestin in quantities sufficient to counteract the action of estrin. When the blood is negative for prolan, it is sometimes possible to accomplish some improvement by the substitutional use of corpus luteum, but when the anterior pituitary sex hormone is found in the blood, operation, radium or x-ray is the only method of treatment which promises any relief.

Roentgen irradiation has been applied to pituitary, ovaries and spleen alone or in combination. The evaluation of pituitary irradiation alone is nearly impossible since it is almost invariably done in combination with the ovaries or spleen. Splenic irradiation seems to have had many advocates some years ago, but most recent data show its loss of popularity. Keene and Payne collected 188 cases of splenic irradiation for functional bleeding, and bleeding was only relieved in 42%. X-ray irradiation of ovaries is reported as satisfactory to stop bleeding but this has many bad after effects. Most authors feel that this form of therapy is only reserved for patients in whom intrauterine radium is contraindicated.

Radium Radium is preferred because its dosage can be regulated
more delicately and the beneficial results are in part due to its local action upon the uterine blood vessels.

Radium is not an entirely satisfactory treatment of menorrhagia. By a series, Dr. Schulze has shown that radium will nearly always control uterine hemorrhage, but that it is occasionally attended with undesirable by effects.

Normal periods are rarely restored, in only 35% of women under 35 and in 7% over this age. In the adolescent group of 6 patients, only one was restored to normal by radium. Only 13% of young women and none over 35, became pregnant after irradiation.

Martial difficulties, which are the result of atrophic changes were often the source of complaint. Satisfactory dosage according to Dr. Schulze, is difficult to establish, since although in general the results are fairly uniform, the individual variation in response to a given dose is so great that the result is unpredictable. For example, they found that amenorrhea resulted from 400 mc. hours, normal periods have been restored by 1525 mc. hours, profuse hemorrhage has continued after repeated treatment with 1024 and 1594 mc. respectively. Women over 35 will generally become amenorrheic or have very scanty or infrequent periods even with small doses. In younger women the prospect of a return to normal is somewhat better. In the adolescent group results with radium have been very poor and it should be used only as a last resort.

Dr. Edward Ewer, Oakland, California, in discussing the use of radium therapy in menorrhagia makes the statement "young women should not be treated unless the bleeding is definitely dangerous
and radium seems preferable to hysterectomy. I find that many women over 40 who have been troubled with excessive flowing, prefer to have the change occur without further delay. To such, I give 1800 mgh. There has been no voluntary complaints of atrophic changes.

Curettage has been useless in my hands, and certainly hormone therapy as we know it today (1937) does not produce the good results obtained with radium in menorrhagia.

J. Morris Slemons, Los Angeles, says that he feels that "radium therapy should be restricted to individuals with whom the production of the menopause would not be an unwelcome sequela. The results cannot be predicted, first, because of difficulty in controlling the dosage—again the anatomical position of the ovaries is too variable.

"Ray treatment" in the opinion of E. Henriksen, Los Angeles is not a dependable form of therapy in the hands of well-trained radiologists and is dangerous in hands of less trained individuals. Menorrhagia of benign nature should be treated by medical, endocrinial, or the use of surgical therapy before resorting to radium in the opinion of Dr. Henriksen.

In his study of radium treatment of abnormal uterine bleeding, Dr. C. Frederic Fluhmann, Stanford Hospital, says he feels that the "intrauterine application of radium or x-irradiation of the ovaries is rarely indicated for uterine hemorrhage in younger women. Dr. Fluhmann points out that irradiation may result in damage to germ-plasm which can manifest itself in succeeding generations. It is true, he says, that many women have had normal children after such treatment, but time only can tell if an injury will not pro-
duce some defect in the offspring of the second or third generations. This has been demonstrated in lower animals. On the other hand, the use of radium for the treatment of functional uterine hemorrhage in women of menopausal age is an effective and comparatively safe method of therapy. Radium is preferred to x-ray since it offers an extensive curettage thus, definitely eliminating the possibility of carcinoma of the fundus uteri.

Contraindications to radium is realized in profoundly anemic patients. It is dangerous in patients who have had a previous pelvic operation since an intestinal loop adherent to the uterus may be seriously damaged by the rays. The highly nervous woman is ill adapted both to radium and roentgen therapy because of the distressing sequelae which frequently attend the induced menopause.

Operative

Burch says that "while surgery has in a few cases aided these disorders of flow, it can only at best be credited as a symptomatic cure. The glandular disturbance is not removed.

Hysterectomy is reserved for those patients who have not responded to less radical measures or those in whom irradiation is contraindicated. Most surgeons will find several instances among their patients where the symptoms have been surgically removed but endocrinopathy remains to invalid the patient".

High amputation of the uterus or wedge-shaped excision of the fundus according to the Bell-Beuttner technique has been advocated. These procedures are desirable in that menstrual function is continued. However, while these procedures reduce the quantity of flow
they do not assure its regularity.

In the presence of functional bleeding, the ovaries frequently contain single or multiple follicular cysts. The results of excision of a single cyst, the puncture of multiple small cysts or unilateral oophorectomy without hysterectomy are so uncertain Keene and Payne believe in their effects upon the bleeding as to make them inadvisable. The same is true of partial resection of a partial cystic ovary.
SUMMARY

Since the exact cause of normal menstrual bleeding is not definitely known, it is difficult to attempt to indicate any one factor in the hormonal disbalance as being responsible for the excessive bleeding. It has been proven, however, that there is a definite interrelationship between the hormone of the pituitary, ovary, thyroid and other glands. Experimental evidence has shown that upsetting this balance by partial resection or destructive irradiation of any one of these glands often results in this condition of excessive hemorrhage. The chief finding in this condition are the absence of corpus luteum in the ovary, hyperplasia of the endometrium, frequent multiple follicular cysts and irregular ripening and shedding of the endometrium, with the finding of excessive amounts of estrin substance in the content of these cysts and no corpus luteum hormone progestin to antagonize its action, the resultant hyperplasia may be expected. Thus, this hyperplasia and progestin lack while the immediate factors in the cause of bleeding, are only the final step in a series which may begin with prolan deficiencies resulting in anovulatory menstruation or with chronic adnexal disease or salpingitis, forming a thick fibrous coat on the ovary which would not allow for the rupture of the follicle and subsequent luteinization. Thyroid hypo or hyperfunction is sometimes the original factor producing a subsequent hormonal disbalance and bleeding.

Some authors, however, feel that the endometrial change seen are not sufficient to account for the hemorrhage and suggest some
bleeding factors—supposedly a pituitary hormone—which in excess might be responsible for the excessive bleeding.

Other investigators feel that the progestin deficiency, the immediate responsible bleeding factors, may in adolescence be explained by the early appearance of the pituitary hormones before the ovary has become active. The cause in active reproductive life, they feel, is explained by follicular cysts and results in earlier chronic pelvic infection, while premenopausal bleeding is probably due to the inability of the senile ovary to form corpora lutea and progestin.

The use of hormonal treatment would on first thought seem the ideal therapy here, however, it must be remembered the injection of hormones is at large only a substitution process and usually does not clear up the factor causing the deficiency.

The use of estrin here has no apparent basis for the system already has an overabundance of this hormone. Progestin while it usually stops the bleeding, would necessarily need be injected before each period to have any effect over a long period. The difficulty in obtaining pure hormonal preparation of the ovary or pituitary make the use of the pregnancy urine prolan or placental extracts the popular choice. Many investigators feel that these by acting through the pituitary or on the ovary will stimulate ovulation and luteal formation and statistics do appear to make this the most successful treatment thus far tried. Various other means of supplying pregnancy urine prolan as pregnancy urine retention enemas or by the injection of blood from pregnancy donors
has been used with some success, however, the methods of ad-
ministration are against these.

Blood coagulates as snake venom, calcium, congo red have been
used with possibly some beneficial effects in stopping bleeding
for the time.

Because the breast apparently inhibites menstruation by con-
trolling estrin during lactations, breast extracts and galvanic
stimulates of the breast have been used and quite good apparent
success reported.

Thyroid extract while producing excellent results in conditions
of thyroid deficiency, seem also to have some ability, in small
doses, to aid other hormones given in conjunction.

Curettage while an excellent diagnostic means and serving well
to stop bleeding until further study and hormonal treatment can be
instigated, is usually not resorted to in puberty where the condi-
tion often tends to disappear as the age of 18-20 is approached.
It is often used in middle-age patients.

Irradiation therapy, while serving in excellent stead in pre-
menopausal bleeding, is seldom used in other cases because of
resulting menopause and other by effects.

Surgery, as hysterectomy is only resorted too when other means
have failed. Rupture of ovarian cysts has had little good results
where tried.

Thus, it can be seen that in functional bleeding there is, as
yet, no sure means of controlling the hemorrhage. Many types of
therapy are being tried with various results in different in-
dividual patients.
BIBLIOGRAPHY


Bishop, P.M., Cook, W.C. and Hampson, A.C. Clinical use of progestin in menorrhagia. Lancet, 1; 139 Jan. 19, 1935

Blair, E. Murray Endometrial Hyperplasia. Canad. M.J., 35; 603-09 Dec. 1936


Burch, J.C. Abnormal and Irregular decline of Estrin Am. Jour. Obst. and Gyn. 25: 826 1933


Collip, J.B. Production of Estus. J.A.M.A. 101-1553 1933


Cronental, J. Treatment uterine bleeding by stimulation of mammary gland with Galvanic current. Zentralb F. Gynak 59: 1288 1935 (yearbook)

Drip, Della G. Editorial Surgery Gyn. and Obst. April 1937


Evans, H.M. Relation of Prolan to anterior Hypophyseal hormones. Amer. Jour. Physiol. 100:141 1932

Fluhmann, C.F. Methods of investigating uterine bleeding. Western Jour. Surgery--Obst. and Gynec. 45:61-71, Feb. 1937

Fluhmann, C.F. Histological Studies of the endometrium J.A.M.A. 93: 1136 1929

Fluhmann, C.F. Estrin deprivation theory of menstruation Endocrinology 20: 318-21 1936


Fluhmann, C.F. Radium Treatment of Abnormal uterine bleeding Calif. and Western Med. 47 101-06 Aug. 1937

Franks, R.T., Goldberger, S. and Spellman, R. Endocrine Diagnosis and Therapy. J.A.M.A. 103: 393-401 Aug. 1934

Franks, R.T. Role of Female Sex Hormones. J.A.M.A. 97:1852 1931


Huskins, R.G. Thyroid on Menorrhagia J.A.M.A. 105: 948 Sept. 1935


Kane, H.F. The Role of Hormones in the cause and treatment of Functional Uterine Bleeding. Virginia Medical Monthly 62: 19 April 1935

Deonard, S.L. The Nature of the substance causing ovulation in the rabbit. Jour. Physiol. 98:406 1931


Mozer, C. and Goldstein. Clinical Endocrinology of the Female. Saunders, Philadelphia 1932


Schulze, M. Menorrhagia--results of radium treatment. Calif. and Western Med. 47: 101-06 Aug. 1937


Traut, H. and Kuder, A. Irregular Ripening and Irregular Shedding

Wiesner, J. Edinburgh Medical Journal 37:73 1930


Witherspoon, J.T. Treatment of Functional puberty Bleeding by Hormones New Orleans Med. and Surg. 86:659-64 1933-34

Witherspoon, J.T. Treatment menstrual Bleeding by the injection of blood of pregnant donors New Orleans Med. and Surg. 86:85-91 1933-34
