THE MANAGEMENT OF ABNORMAL VAGINAL BLEEDING

H. J. STANDER, M.D., F.A.C.S., C.T. JAVERT, M.D., and K. KUDER, M.D.,
New York, New York

ABNORMAL vaginal bleeding is a gynecological complaint frequently encountered by the general practitioner. All age groups are represented, from before puberty, through the reproductive cycle, at the menopause, and in the postclimacteric period. The average physician often undertakes the management of such bleeding as an office procedure, and after a period of time often sends the patient to a hospital. Over 40 per cent of 8,216 patients admitted to the gynecological service of the Woman's Clinic of the New York Hospital had a history of abnormal vaginal bleeding, while in approximately half of these menorrhagia and metrorrhagia constituted the chief complaint. The actual loss of blood over long periods of time, the associated weakness and debility, the inconvenience to the patient of increased and continued flow, as well as the danger of an underlying malignancy, make such abnormal bleeding a most important problem.

The causes of abnormal bleeding are numerous and have been given repeatedly in the literature. Included are myomas, polyps, ovarian tumors, cervical and vaginal erosions and tumors, carcinoma, and the gestational states including ectopic pregnancy and abortion.

The relative frequency of occurrence of the causes of bleeding varies markedly with the age groups. Shortly after birth, withdrawal of the maternal estrogens may cause vaginal bleeding in the offspring, while during the first decade of life ovarian tumors are the predominant cause, tumors of the pituitary, adrenal and pineal coming next in order of frequency. Only very rarely do we encounter malignancy of the genital tract in infancy and childhood. During the second decade, or period of sex development, endocrine imbalance assumes first importance, to be followed by inflammatory lesions, and occasionally by benign ovarian tumors. Myomas and malignant tumors are almost too rare to be mentioned in this age group. In the childbearing period, gestation, pelvic inflammatory disease, myomas, cysts of the ovary, endocrine disturbances and malignant growths of the genital tract, constitute the order of incidence. In the fifth and sixth decades of life, menopausal bleeding and malignant growths are the outstanding causes. Carcinoma of the cervix is particularly prevalent in the fifth and carcinoma of the body of the uterus in the sixth decades. After the age of sixty, malignancy and benign polyps are the outstanding causes, with carcinoma of the cervix, corpus uteri or ovaries to be kept in mind. Granulosa cell tumor of the ovary may precipitate bleeding, as do also atrophic vaginitis or inflammation.

It is quite apparent, then, because of the variety of etiological factors, that in all cases of abnormal bleeding a thorough search for the cause must precede any and every attempt at treatment. With the development and growth of "endocrine clinics" in virtually all departments and specialties of medicine it has become more and more evident, during the past ten years, that this all important prerequisite of thorough examination, including pelvic examination by a competent gynecologist, and whenever indicated vaginal smears, biopsy or curettage, is not followed. How often these days do we not see women who had had all types of indiscriminate "endocrine therapy," without a correct diagnosis of the cause of the bleeding? It is our opinion that before reliance is placed wholly on pregnandiol excretion values and the quantitative results for estrogen and pituitary hormone levels, organic causes of bleeding *must* be eliminated. Unfortunately, the urine and blood determinations for the various hormones are as yet not of sufficient practical value to indicate the proper treatment in the majority of cases.

A careful history of the character and amount of bleeding; thorough pelvic examination, under anesthesia if necessary; visual inspection of the cervix, with biopsy if in the least suspicious; vaginal smears and examination of the endometrium, by either biopsy or curettage, are our best means of establishing a diagnosis. By these methods, cervical and uterine polyps, chronic cervicitis and endometritis, myoma uteri, hyperplasia of the endometrium, salpingitis, cysts and tumors of the ovary, and malignant disease of the cervix and corpus may be diagnosed. The treatment of each of these, with the possible ex-

From the Department of Obstetrics and Gynecology, Cornell University Medical College and New York Hospital.

Read before the Dallas Southern Clinical Society, Dallas, Texas, March, 1942.

TABLE I.—CAUSES OF VAGINAL BLEEDING IN GYNECOLOGIC PATIENTS SEPTEMBER 1, 1932 TO DECEMBER 31, 1940

	Number	Per cent
Undetermined	865	24.9
Myoma uteri	854	24.6
Hyperplasia endometrium	534	15.3
Polyp, endometrial	344	9.9
Cervicitis and erosion	221	6.4
Polyp, cervical	210	6.0
Irregular shedding	135	3.8
Adenomyoma	102	2.9
Carcinoma cervix	75	2.2
Carcinoma uterus	72	2.0
Endometritis	52	1.5
Sarcoma uterus	4	0.11
Total	3468	99.6
Total number of patients	8,216	
Patients with bleeding	3,468	42.2

ception of endometrial hyperplasia, is fairly specific, although unfortunately not always curative.

From Table I it will be seen that in only three-quarters of our gynecological patients with abnormal vaginal bleeding was a definite diagnosis established, while in the remaining one-quarter, or 865 women, we were unable to determine the etiology of the bleeding. Of the known causes, myoma uteri accounted for the hemorrhage in 854 women, or 24.6 per cent of the total series, while hyperplasia of the endometrium ranked next in order of frequency, being responsible for 15.3 per cent of the cases.

The term "functional bleeding" has been used with greatly varying interpretations. It is our contention that this term should be limited to those cases in which no organic lesions, such as malignancy, myomas, polyps, or inflammation, are present. If used in this limited sense, "functional bleeding" would include the groups "cause undetermined," "hyperplasia," and "irregular shedding" in Table I, and thus account for 44 per cent of all the cases of abnormal bleeding. It may be advisable, as we gain more information, to limit even further the use of this term, and confine it to the group of "causes unknown." In Table II we have included under "functional bleeding" hyperplasia and irregular shedding. In only slightly over one-third of these patients with functional bleeding, was hyperplasia of the endometrium found at operation, while irregular shedding of the endometrium accounted for less than 10 per cent. The diagnosis was undetermined in over half of these patients.

The treatment of the gross pathological causes for bleeding will not be discussed in this paper. It must be stressed, however, that no treatment of abnormal vaginal bleeding should be undertaken unless and until a thorough investigation of the patient has been made, benign as well as malignant tumors ruled in or out, and a diagnosis, if possible, established.

If the menorrhagia, metrorrhagia, or polymenorrhea is disclosed by the history and physical examination, vaginal smears and endometrial biopsy may reveal a hyperestrin condition. Granting that organic causes are not present, dilatation and curettage will often effect a cure. It is, of course, essential that any thyroid deficiency, as shown by the basal metabolic rate, be corrected. This applies likewise to the body weight and anemia, in which cases proper dietary measures may be indicated. Should dilatation and curettage, often repeated, once or twice prove of no avail, endocrine therapy may be tried. It is seldom that radical treatment is instituted.

From Table III it is noted that in 94.1 per cent of the patients with hyperplastic endometrium, the operative treatment was minor, i.e., a dilatation and curettage. In only 5.9 per cent of these patients was a major operation performed, and in most of these the hyperplasia was a secondary finding. This holds almost equally true for the patients who showed irregular shedding of the endometrium. In the majority, or 66.6 per cent, of our gynecological patients with abnormal bleeding, dilatation and curettage alone was performed. Furthermore, a striking comparison is seen between the organic and "functional" bleeding cases; minor operative procedures were performed in about half of the former and in 80 per cent of the latter.

Not infrequently, no gynecological pathology can be found to explain the bleeding. This occurs, as shown in Table I, in about 25 per cent of our patients. These cases usually have had hormonal substitution therapy, often without effect except perhaps a depletion of the patient's finances. It should also be borne in mind that hypertension *per se* may be an accessory factor in abnormal uterine bleeding. It seems desirable to scrutinize certain known causes of bleeding elsewhere in the human body, i.e., skin purpura,

TABLE II.—CAUSES OF "FUNCTIONAL BLEEDING"

	Number	Per cent
Undetermined	865	56.3
Hyperplasia endometrium	534	34.8
Irregular shedding	135	8.8
Total	1534	99.9

bleeding gums, and melena, and see if they can be used to explain certain cases of abnormal vaginal bleeding.

The reason for such a departure from the conventional consideration of menorrhagia and metrorrhagia is represented by a small but important nucleus of 20 patients with uterine bleeding, ranging in age from 15 to 47 years of age. These patients were investigated from the standpoint of deficiency in vitamins C and K. There is no doubt as to the relationship of these vitamins to the bleeding and clotting mechanism. Very little attention has been paid to vitamins in the literature from the standpoint of uterine bleeding, probably because they have been overshadowed by the endocrines both theoretically and therapeutically.

Vitamin C and prothrombin determinations were performed on the 20 patients and the results are shown in Table IV. The average value for vitamin C was 0.43 milligrams, according to the Mindlin and Butler technique (normal value, .5–1.4 mgm.). The range varied from .00 to 1.1 milligrams, with 70 per cent of the patients below the normal range of 0.5 to 1.2 milligrams. The few cases with normal values invariably had a low prothrombin concentration, and vice versa. The average prothrombin concentration in our 20 patients was only 50 per cent of normal; it was below normal in 79 per cent. In these determinations we employed the Warner, Brinkhous, and Smith technique by which normal patients have a range of 70 to 100 per cent. The majority of our bleeding patients were below the normal range.

What rôle, if any, does a deficiency in vitamins C and K play either separately or jointly in producing abnormal vaginal bleeding in nonpregnant women? Knowledge of the state of the endometrium is important, and every type of endometrium was represented in the 20 patients as follows: proliferative, 5; secretory, 7; hyperplasia, 6; and endometritis, 2. Several had associated pathology such as myomas or polyps. What is the basis for the bleeding in these patients with evidence of hypovitaminosis C and K?

Giedosz and Rychlik report that scorbutic guinea pigs do not develop ovarian follicles.

TABLE III.—TREATMENT OF "FUNCTIONAL BLEEDING"

Causes	Operations: Major Per cent	Operations: Minor Per cent	Non-operative Per cent
Undetermined	14.6	69.9	15.3
Hyperplasia endometrium	5.9	94.1	0.0
Irregular shedding	11.9	88.1	0.0

TABLE IV.—INITIAL CURETTAGE AND SUBSEQUENT TREATMENT AND COURSE IN 495 PATIENTS WITH "FUNCTIONAL BLEEDING"

Treatment or course	Causes of Bleeding: Undetermined	Causes of Bleeding: Hyperplasia	Causes of Bleeding: Irregular shedding	Number of cases	Per cent
One curettage or more	153	109	21	283	57.2
Curettage and menopause	38	33	8	79	15.9
Curettage and pregnancy	25	18	1	44	8.9
Curettage and endocrine therapy	3	19	0	22	4.4
Curettage and radical therapy*	24	41	2	67	13.5
Total	243	220	32	495	99.9

*Patients over 40 years of age.

Deficiency in vitamin C makes those present undergo atresia. Normally, the corpus luteum contains large quantities of vitamin C according to both Ley and Vogt. Biskind and Glick obtained large quantities of vitamin C in the corporea lutea of cows and suggested that it was necessary for the formation of progesterone. Mendive and Deulofeu discovered large amounts in the hypophysis and thyroid gland. However, there is not sufficient evidence to justify the theory that deficiencies in vitamin C can alter the hypophyseal-thyroid-ovarian relationship and so indirectly account for functional bleeding. It may perhaps play a more direct rôle on the spiral arteries of the endometrial glands allowing bleeding to take place much as bleeding gums, nosebleeds, and skin bruising occur in patients with a deficiency in these vitamins.

The rôle of vitamin K in maintaining a satisfactory prothrombin concentration is now well established. The importance of prothrombin in the clotting mechanism needs no discussion. It is conceivable that the onset of bleeding precipitated by a normal menstrual cycle might be prolonged or unusually heavy if an inadequate amount of prothrombin or vitamin C is not available. In this era of drug-counter eating, with a half hour for lunch, the nutrition of these women is certainly below par. Some of these patients also gave a history of using mineral oil and olive oil. Singleton employed dehydrated young grasses for its vitamin K content in the treatment of menorrhagia with satisfactory response. His experience together with our use of vitamins C and K seem to indicate that these vitamins have therapeutic value in this condition.

The use of vitamins C and K was limited to the 20 patients referred to. Cevitamic acid, 100

TABLE V.—TYPES OF TREATMENT EMPLOYED IN 372 PATIENTS WITH "FUNCTIONAL BLEEDING"

Treatment	Total number of cases	Patients cured as shown by follow-up period of 1 to 4 years	
		Number	Per cent
Curettage	283	201	71.0
Radium	49	46	93.8
Hysterectomy	13	13	100.0
X-ray	5	5	100.0
Hormones	22	4	18.1
Total	372	269	

milligrams daily orally, and 100 cubic centimeters of orange juice were given until the vitamin C level in the blood was normal. Vitamin K was given hypodermically until a satisfactory prothrombin concentration was obtained, to be followed by oral administration of vitamin K. The follow-up results are as follows: Of 8 cases treated with vitamin C and K following curettage, 6 were definitely improved, as shown by follow-up for 3 to 15 months. In 2 it is too early to determine result. The beneficial value of the curettage alone is, of course, to be borne in mind. Of the untreated control cases, 5 improved following hysteromyomectomy or radium, 3 were not improved, and in 4 it is too early to state result.

From these considerations, it would appear that an accurate and complete history, including dietary habits, is of great importance. As stated, a careful pelvic examination is imperative in addition to the general physical examination. Many practitioners hesitate to examine the female genitalia because of supposed consideration for the patient, while some postpone examination while vaginal bleeding is present. Such delay means further blood loss, and the possibility that the patient may not return for examination. We have no hesitation in examining the bleeding patient on the first visit unless pregnancy is suspected.

It has been our policy to admit bleeding patients to the hospital for a diagnostic curettage regardless of age or underlying gynecological pathology before instituting medical treatment. An occasional patient with an obvious tumor is subjected to laparotomy without the preliminary curettage. However, the endometrium is scrutinized in the operating room before the abdomen is closed.

Many patients come to us from physicians after unsuccessful attempts to correct the bleeding with hormonal injections or even x-ray irradiation, without a preliminary curettage having been performed. Needless to say, many of these had a malignant neoplasm. Such practice cannot be condemned too strongly.

In 1938 we studied 495 patients with functional bleeding. We have completed a follow-up study on these patients, and the types of treatment with results are presented.

From Table IV it will be noted that every patient had an initial curettage, primarily, of course, as part of the diagnostic procedures. Thereafter, a certain number (15.9 per cent) passed through an uneventful menopause; 8.9 per cent had subsequent pregnancy which was undoubtedly of assistance in effecting a "cure"; endocrine therapy was given to 4.4. per cent, and 13.5 per cent (over 40 years of age) had radical treatment. The radical treatment consisted of the intracavitary administration of radium, or hysterectomy, or the use of x-rays.

The follow-up results in 372 of the 495 patients are shown in Table V. It will be seen that curettage alone gave a "cure" rate of 71 per cent. The number of patients treated with hormones is too small to permit of any definite conclusion. The small percentage of our patients treated with endocrines is to be explained on the basis of the unsatisfactory results we obtained during the early years of the period studied, 1932 to 1938. In those days we relied primarily upon antuitrin-S and pregnancy urine extracts. It is only fair, therefore, to state that as the newer preparations (progesterone, stilbestrol, etc.) have appeared, an increasing number of patients with functional bleeding have received endocrine therapy. Since then, a sufficient period of time has not elapsed for a final evaluation of our end-results in endocrine treatment.

In Table VI is given the distribution of patients receiving one, two, three, or more curettages. Of significance is the fact that a far smaller percentage of cures is effected after two, or even smaller after three or more curettages, as compared with the results after one curettage, 71 per cent.

Hysterectomy is, indeed, radical treatment for abnormal vaginal bleeding of the functional type. It is necessary to stress the dangers, as well as the sequelae of such radical treatment, especially in the woman in her second or third decade of life.

SUMMARY OF TREATMENT IN "FUNCTIONAL" BLEEDING

Curettage. In the treatment of functional bleeding the first step is curettage. This is essential to

the diagnosis of the condition and is often followed by improvement, as shown in Tables V and VI. Reviewing 495 cases of functional bleeding which had occurred in our gynecological service during 6⅓ years ending December 31, 1938, and followed up to March 1, 1942, we find that curettage alone resulted in cure or definite improvement in 71 per cent. Curettage plus other methods of treatment gave improvement or cure in varying percentages, as outlined here. The other methods of treatment involve the use of thyroid, snake venom, hormone, and vitamin administration, radiation, and hysterectomy.

Thyroid. There can be little doubt that a low basal rate is at times associated with uterine bleeding, due to the close interrelationship of the various endocrine glands, pituitary, thyroid, adrenals, and ovaries. It is, therefore, evident that any hypofunction of the thyroid gland should be corrected.

Vitamins. There is little doubt in our minds that a deficiency in vitamins C and K plays a rôle in the production of excessive uterine bleeding in certain patients, in whom all other causes of bleeding are absent. It may be that such a deficiency is at times operating in conjunction with a hormone imbalance. It is advisable, therefore, that in such cases, in which the usual endocrine therapy fails, the blood levels C and prothrombin be determined. Should a definite deficiency be present, an adequate supply of C and K, in the form of cevitamic acid (100 mgm. daily), orange juice and synthetic K (from 5 to 50 mgm. orally or intramuscularly) be administered to the patient.

Snake venom. Snake venom acts upon the walls of the arterioles, decreasing or controlling bleeding in certain cases. Moccasin venom in 1:3000 dilution is given subcutaneously daily in doses starting with ½ cubic centimeter and increasing slowly to 1 cubic centimeter. We have had many failures with this method, but do use it in certain cases in which other therapy fails. The results are varying, and do not permit a definite conclusion, although we may state that we have had improvement in some patients treated with snake venom, after previous failures with other types of therapy.

Radiation. In our opinion, x-ray treatment should be used only in women beyond the childbearing period and in whom other forms of therapy are of no avail. It is not our practice to attempt to regulate menstruation in girls or young women by radiation, because of the uncertainty of the relationship between dosage and result. On the other hand, Pemberton, as well as Keene and Payne, reported good results in young women

TABLE VI.—ONE TO FOUR YEAR FOLLOW-UP RESULTS AFTER CURETTAGE ONLY IN 283 PATIENTS WITH "FUNCTIONAL BLEEDING"

Number of curettages	Number of patients			Total
	Cured	Improved	Not improved	
1	168	22	34	224
2	31	2	15	48
3 or more	2	1	8	11
Total	201	25	57	283
Per cent	71.0	8.8	20.1	

with small dosages of radium, ranging from 200 to 400 milligram hours. We have hesitated to resort to this form of treatment in women not close to, or at, the menopause. When we have used radiation, it has been confined to those past the childbearing period and in dosage sufficient to cause cessation of ovarian function, usually 1500 milligram hours of intracavitary radium. As shown in Table V, bleeding recurred in 3 patients receiving radium. If x-ray radiation is used for the production of permanent amenorrhea, the dosage is usually about 400 r through two portals, one suprapubic and one sacral. We have not resorted to radiation of the pituitary gland for the control of functional bleeding.

Endocrine therapy. There is evidence to support the conclusion that a hyperestrin condition or a deficiency of progesterone is associated with certain cases of functional bleeding, and thus there exists a rational basis for endocrine therapy in this condition.

This type of therapy may be briefly grouped as follows: (1) anterior pituitary extract; (2) chorionic gonadotropic hormones obtained from pregnancy urine and pregnant mares' serum; (3) sex hormones, the estrogens and progesterone; (4) androgens.

Experience with anterior pituitary extracts is too limited to allow any concrete statement at the present time. A few authors, including Severinghaus, Mayer, and others, have reported short series of cases with encouraging results. Our own experience has been disappointing and at present we are not using these extracts. The same may be said for pregnancy urine, or antuitrin-S, or follutein. There is also doubt in our minds as to the efficacy of pregnant mares' serum.

The best results with endocrine therapy appear to have been obtained with the female sex hormones, estrogen, and progesterone. The natural estrogens (estrone, estriadol, estriol) and also the synthetic drug stilbestrol, and the corpus

luteum hormone progesterone, have been used in combinations by some, while others rely mainly on the latter. Estrogens, or stilbestrol alone, likewise have been employed, as we believe, misguidedly.

The combined therapy consists of a course of estrogens followed by progesterone. The procedure, in general, is to start 6 or 7 days after the cessation of bleeding with 10,000 to 20,000 international units (I. U.) of estrogen daily for a period of 2 weeks, after which progesterone (5 I.U.) is given daily for one week, or until bleeding occurs. This type of treatment, supportive in character, tends to bring about normal menstrual cycles and so control the excessive bleeding. It must be pointed out that the menstrual cycle is normally fairly irregular, and such cyclic endocrine therapy in many instances would be most inadvisable, except when one deals with excessive bleeding (functional) or marked menstrual irregularity which is associated with sterility.

Several recent reports have appeared on the use of the nonhormonal drug stilbestrol in the control of functional bleeding. Palmer, in a study of 31 patients, advises 1 milligram of diethylstilbestrol daily for 7 days, then 5 milligrams daily for 7 days, and then smaller amounts (0. 3 mgm.) daily for 10 days, or until bleeding starts. Some advise even larger doses of this drug given over longer periods. We have had no experience with stilbestrol in the treatment of functional bleeding. We are as yet not convinced that this form of therapy is devoid of all danger.

We have relied more on progesterone treatment in these cases of estrogenic (anovulatory) bleeding. It is our practice to give 5 milligrams of progestin daily for several days before the expected period. Some cases respond to this therapy.

There does not appear to be sufficient evidence at the present time for the use of androgens in the treatment of functional bleeding in the young woman. It should be stated, however, that Geist and his coworkers report favorable results in a fairly large series of cases. The effects of the androgens are due to their stopping or overriding of ovarian function, and so the danger of virilization should be borne in mind.

CONCLUSIONS

1. A definite diagnosis as to the cause of uterine bleeding is essential to proper treatment.

2. A complete history, thorough physical examination (including pelvic examination and visualization of the cervix), vaginal smears, and endometrial biopsy or curettage are essential to accurate diagnosis.

3. Vitamin C and K determinations may reveal marked deficiencies, which in certain cases of undetermined etiology may be responsible for the excessive bleeding.

4. A basal metabolic rate determination may indicate hypothyroidism, which likewise may be linked with the etiology of the bleeding.

5. Proper treatment must be directed to the cause of the bleeding, if that is established. Cervical erosions, polyps, myomas, genital malignant growths, and pelvic infection must be treated, if found to be the cause of the bleeding.

6. If deficiency of thyroid secretion or of vitamins C and K is present, these must be corrected.

7. In functional bleeding dependent upon hyperestrin conditions, endocrine therapy, either complemental cyclic treatment (estrogens and progesterone) or progesterone is indicated.

8. In the control of functional bleeding, radiation therapy should be reserved for the woman past the childbearing period (40 years of age).

9. Hysterectomy should be our last resort in the treatment of functional bleeding and, like radiation, used only in the older group of women.

10. It should be borne in mind that the menstrual cycle may be, normally, quite irregular and also that so-called "functional bleeding" may be self limited.

11. The routine use of endocrine preparations for the control of uterine bleeding, without an accurate diagnosis as to the cause of the hemorrhage, cannot be too strongly condemned.

REFERENCES

1. Biskind, G., and Glick, D. J. Biol. Chem., 1936, 113: 27.
2. Elliot, M., Isaccs, B., and Ivy, A. Proc. Soc. Exp. Biol., N.Y., 1940, 43: 240.
3. Giedosz, B., and Rychlik, W. C. rend. Soc. biol., 1936, 123: 1226.
4. Hamblen, E. C. Surg. Gyn. Obst., 1942, 74: 490.
5. Hendriksen, E. Am. J. Obst., 1941, 41: 179.
6. Javert, C. T., and Macri, C. Am. J. Obst., 1941, 42: 409.
7. Ley, L. Münch. med. Wschr., 1937, 84: 1814.
8. Mendive, J., and Deulofeu, V. Zschr. physiol. Chem., 1936, 236: 208.
9. Mindlin, R., and Butler, A. J. Biol. Chem., 1937, 122: 673.
10. Palmer, A. Am. J. Obst., 1941, 41: 1018.
11. Papanicolaou, G., and Traut, H. Am. J. Obst., 1941, 42: 193.
12. Singleton, J. M. Kansas City M. J., March, 1940.
13. Vogt, E. Münch. med. Wschr., 1934, 81: 791.
14. Warner, E., Brinkhous, K., and Smith, H. Am. J. Physiol., 1935, 114: 667.