

OBSERVATIONS ON HISTOPATHOLOGICAL CHANGES IN THE UTERUS IN DYSFUNCTIONAL UTERINE HAEMORRHAGE

by

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Dysfunctional uterine haemorrhage is a condition frequently encountered in gynaecological practice. Though the condition has been extensively studied in recent years, it has remained imperfectly understood. The conventional definition of dysfunctional uterine haemorrhage, i.e. irregular uterine bleeding in absence of pelvic pathology by ordinary clinical examination, is open to objection, because better diagnostic aids, such as curettage, biopsy, vaginal smears, culdoscopy and laparotomy, would reveal a definite pelvic pathology in many cases diagnosed as dysfunctional uterine bleeding. Bourne and Williams recognised a condition which they called 'true functional uterine bleeding', and in this condition they included such endometrial conditions as result from disturbed endocrine influence and in which there is no departure from the normal by ordinary histological examination. Novak and Jones have recently defined, dysfunctional uterine bleeding as abnormal uterine bleeding unassociated with

tumour, inflammation or pregnancy. It is significant to note that more recently the term "ordinary clinical examination" associated with the conventional definition of dysfunctional uterine haemorrhage is giving place to the term "ordinary histological examination", and that histological study of the endometrium is receiving more importance in the elucidation of the aetiology.

The histopathology of dysfunctional uterine haemorrhage has been under investigation for long. Schroder first described in detail "endometrial hyperplasia" as a definite histopathological entity. This endometrial condition is also known after him as "Schroder's disease". Later, Traut and Kuder described accurately two other metropathies. One of them, called "irregular shedding", had been described earlier by Pankow, and the other was described *de novo* as "irregular ripening". More recently dysfunctional uterine bleeding has been extensively studied by Sutherland who analysed 1,000 cases diagnosed as dysfunctional uterine bleeding by ordinary clinical examination. He found pathological lesions, such as chronic endometritis, uterine polyp, endometrial tuberculosis and malign-

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nant disease in 139, i.e. in 13.9% of the cases. In the remaining true cases of functional uterine bleeding, he found endometrial hyperplasia in 30.8%, irregular shedding in 1.5%, irregular ripening in 3%, and endometrial atrophy in 1.1%. In the majority, i.e. in 63.2% of his cases, however, the endometrium looked normal. Thus five main types of endometrial pictures, i.e. normal looking endometrium, endometrial hyperplasia, irregular shedding, irregular ripening and atrophic endometrium have come to be recognized in dysfunctional uterine haemorrhage. While working on hormonal therapy based on the percentage of cornified cells in the vaginal smear, Shah and Dave found atrophic endometrium in 5%, proliferative endometrium in 26.5%, hyperplastic endometrium in 58% and secretory endometrium in 10% of their 60 patients of dysfunctional uterine bleeding. The authors found tuberculous endometritis in 10% of the biopsy specimens examined. There is no correlation of these endometrial changes with the clinical features of the disease. Te Linde remarked that dysfunctional bleeding may be present in association with such a variety of microscopic pictures that it is obvious that the bleeding is not inherently bound up aetiologically with the microscopic picture and that the actual causal mechanism of the excessive and/or irregular flow is not understood. However, a disturbance in the hypophysial-ovarian-uterine relationship is generally taken to be the cause of dysfunctional uterine bleeding. This disturbance would obviously affect the composition and quantity of

hormones in the blood, and many authors including Chandri Kar found hormone therapy very useful in the treatment of dysfunctional uterine bleeding. However, there is no practical and reliable laboratory technique at present for assessment of hormone level in blood. Histological examination of the endometrium can give indirect evidence of hormonal status of the endometrium, and has been attempted by various investigators with a view to explain the exact mechanism of bleeding from the endometrium. So far, the histological investigation has not been able to reveal the secrecy which surrounds the aetiology of the disease. More recently histochemical changes in the endometrium have been studied to explain the aetiology of dysfunctional uterine bleeding. Shahani, Chitnis and Purandare remarked that histochemical changes in the endometrium in respect of glycogen and alkaline phosphatase can throw a great deal of light on the physiology of uterine mucosa.

In the present investigation endometrial changes in cases of dysfunctional uterine bleeding have been examined in order to understand their clinical significance and hormonal relationship with bleeding. As the endometrial function is a variant of the ovarian function, ovarian tissues have also been examined in order to note the changes in them, particularly in regard to the follicular and luteal changes, so that their significance vis-a-vis endometrial changes and functional uterine bleeding, could be understood. The significance of age distribution and parity was analysed in order to note their possible aetio-

logical relationship with functional uterine bleeding.

Selection of Cases and Processing of Endometrial Tissue for Examination

The 100 cases selected for the present investigation were admitted at random as they came to the out-patient's department of the Hospital for Women, Patna, and were diagnosed by the conventional method. No attempt was made to secure the endometrial tissue at particular times in the menstrual cycle, for this would necessitate keeping the patients in the ward too long. The uterine and ovarian tissues were obtained for study when the patients had undergone hysterectomy, and in other patients the endometrial tissue was obtained by curettage. Immediately after removal, the endometrial and ovarian tissues were fixed in 10% formalin solution and were processed and differentially stained in haematoxylin and eosin for histological examination.

Results of Investigation

1. *Incidence of Dysfunction Uterine Haemorrhage in India.* As gynaecological clinics are very few, located mostly in large towns, and as economic conditions generally prevent patients from coming to these clinics for advice, hospital records of incidence may only give a rough indication of the status of the disease in the population in the neighbourhood. During the last five years, the annual admission of patients at the Hospital for Women, Patna, varied from 2,206 to 2,837 and the average incidence of dysfunctional uterine haemorrhage was 7.8%. This figure, as expected,

is slightly, lower than that recorded at large clinics of the West.

2. *Age Distribution in Functional Uterine Haemorrhage.* Dysfunctional uterine haemorrhage is a disease which occurs at menarche and throughout the child-bearing age, being most frequently encountered between 40 and 45 years. Some authors have reported that it occurs frequently just after menarche as at that time the cyclic relationship between the pituitary and the ovary is not fully established. The age incidence in the present series of patients is detailed below in Table 1, and graphically represented in Figure 1.

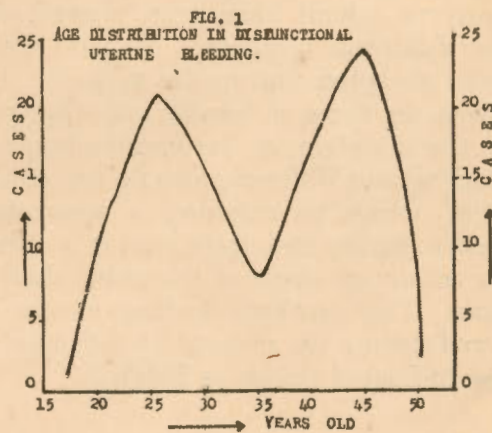


TABLE I
Age Distribution in Dysfunctional Uterine Bleeding

Age group years	No. of patients	Percentage	Average age years
15-19	1	1	18
20-24	10	10	22
25-29	22	22	26
30-34	12	12	30
35-39	8	8	35
40-44	19	19	41
45-49	25	25	46
50-54	3	3	50
Total	100		

The figures in Table 1 indicate that the disease can occur at any age after menarche until menopause, and that it occurs throughout the child-bearing period. Fig. 1 indicates that there are two peaks in the age distribution curve, one near 25 years of age and the other near 45. Shaw noted a similar two-peaked age distribution curve.

3. Occurrence of Histologic Types in Dysfunctional Uterine Bleeding.

As discussed earlier, endometrial hyperplasia, irregular shedding, irregular ripening and atrophic endometrium are the different histologic patterns which have been described by different workers. It has also been accepted that in the majority of the cases there is hardly any change in the histology of the endometrium. Bourne and Williams also do not consider irregular ripening a separate disease entity and opine that it is only an advanced stage of irregular shedding. The histologic findings encountered during the present investigation are indicated below in Table 2.

TABLE II
Histologic Findings in Dysfunctional Uterine Bleeding

Type of endometrium	No. of cases
Apparently normal endometrium ..	56
Endometrial hyperplasia	29
Chronic endometritis	10
Irregular shedding	3
Chorionic-epithelioma	1
Products of conception	1
Total	100

From Table 2, it appears that the incidence of normal looking endometrium, hyperplasia, chronic endometritis and irregular shedding nearly agrees with that of Sutherland. No serious attempt was made in the present investigation to separate an endometrium that would closely agree with the histologic picture of irregular ripening from the endometrium of irregular shedding, and it is likely that for this reason the incidence of irregular shedding is slightly higher than that noted by Sutherland. No case of atrophic endometrium was, however, encountered. It would also appear that in spite of the best effort to exclude pregnancy, it is likely to be included among the cases of functional uterine bleeding, unless biological pregnancy tests are carried out as a routine for confirming pregnancy. Obviously, however, according to the accepted definition of functional uterine bleeding, the single case, in which products of conception were found, had to be excluded from the purview of the present investigation.

The histologic picture in the main histologic types was by no means uniform. There were variations as indicated below in Table 3.

It would appear from Table 3 that the incidence of chronic endometritis which is rather high may be associated with any of the main histologic types. No attempt was made in the present investigation to identify the different inflammatory states. It is likely that culture of the organisms or guineapig inoculation would have indicated the association of tuberculous endometritis in some of these cases.

TABLE III

Variation in Endometrial Picture in Main Histologic Types of Dysfunctional Uterine Haemorrhage

Types of variation in the endometrium	No. of cases
Normal looking endometrium	50
Normal endometrium with chronic endometritis	7
Normal endometrium with exaggerated oestrin phase	6
Normal endometrial hyperplasia	23
Hyperplasia with chronic endometritis	3
Polypoidal hyperplasia	4
Hyperplasia with endometriosis	2
Total	95

In one case, besides endometriosis there was a very early stage of leiomyoma in the uterine wall.

In all cases the coiled arterioles were found to be rather thick and dilated near the surface.

4. *Histology of Endometrium in Relation to Clinical Types.* Dysfunctional uterine bleeding is often classified in relation to the time in the cycle, but no relationship of the clinical types of bleeding with the histologic varieties has generally been found. The types of endometrium encountered in the different varieties are indicated below in Table 4.

TABLE IV

Histology of Endometrium in Different Types of Dysfunctional Bleeding

Type of endometrium	Total cases	Irregular or continuous bleeding		Menorrhagia		Poly-menorrhoea	
		No.	%	No.	%	No.	%
Normal endometrium	56	16	29	25	46	15	25
Endometrial hyperplasia	29	10	34	14	48	5	18
Irregular shedding	3	—	—	3	100	—	—
Total	88	26	29	42	48	20	23

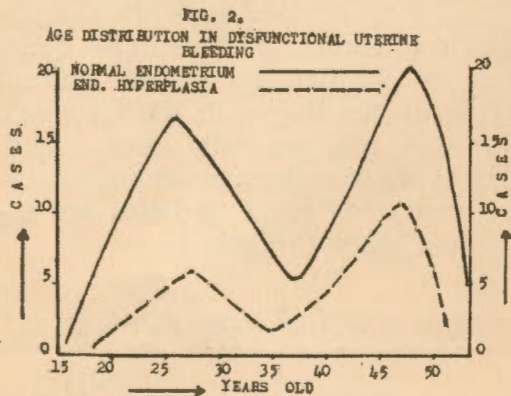
In over 9.5% of the normal looking endometria, an exaggerated oestrin phase was found. There was a much larger number of glands of about the same size than normally found in the oestrin phase. This picture gave a strong impression of occurrence of an active glandular change in the endometrium prior to its differentiation into a "swiss cheese" pattern.

Among the 32 cases of endometrial hyperplasia, polypoidal hyperplasia was present in 12.5% and endometriosis was associated in over 6%.

It would appear from Table 4, that normal endometrium and endometrial hyperplasia have no particular affinity to a particular type of bleeding. The different types of bleeding are about equally distributed among the two histologic groups. All cases of irregular shedding, however, had menorrhagia. These results agree with those of other workers.

5. *Distribution of Main Histologic Types in Different Age Groups.* In view of the fact that there are two peaks in the age distribution curve in

Figure 1, it was felt desirable to know which type of endometrium was responsible for this type of curve. The distribution of the cases under the main histologic types and in the different age groups was, therefore, tabulated below in Table 5, and graphically illustrated in Figure 2.



From Table 5 and Figure 2, it would appear that the distribution of cases according to age in the two main histologic types, i.e. normal endometrium and endometrial hyperplasia, followed the same pattern, suggesting common aetiology of bleeding in the two histologic types.

6. *Parity in Relation to Main Histologic Types.* There were 20 nulliparous and 77 parous patients in the series under investigation. The distribution of normal and hyperplastic endometrium in the two series is indicated below:

From Table 6, it would appear that though parous patients predominated, normal looking endometrium was relatively more common than endometrial hyperplasia in the

TABLE V
Distribution of Different Histologic Types of Endometria in Different Age Groups

Age group years	Normal endometr.		End. hyperplasia		Irreg. shedding	
	No. cases	Average age	No. cases	Average age	No. cases	Average age
15-19	0	0	1	18	0	0
20-24	6	22	3	22	1	34
25-29	15	25	6	27	1	25
30-34	9	30	3	31	—	—
35-39	5	35	2	36	—	—
40-44	6	41	7	41	1	40
45-49	21	46	11	46	—	—
50-54	1	50	2	50	—	—
Total	63	—	35	—	3	—

TABLE VI
Distribution of Histologic Types in Relation to Parity

Patients	Total cases	Normal endometr.	Endometr. hyperplasia
Nulliparous	20	85%	15%
Parous	77	65%	35%

nulliparous group. In the parous patients also normal looking endometrium was relatively more common than endometrial hyperplasia but with a reduced margin. For example, the difference between the percentage incidence of the two histologic types was 70 in the nulliparous, but only 30 in the parous patients. It is, therefore, obvious that some other factor comes into play in the nulliparous patients, which is responsible for more functional bleeding in them without causing any appreciable change in the endometrium. This fact is further borne out by the pattern of distribution of parous and nulliparous patients in the different age groups as detailed below in Table 7.

the age group of 21-30 years. In the same age group the nulliparous patients with endometrial hyperplasia were much less common than parous patients with endometrial hyperplasia. Obviously, most of the nulliparous patients were in the age group in which emotional upset may be thought to be more common.

7. *Endometrial Pattern in relation to Ovarian Changes.* Seventeen specimens of ovarian tissue were available for examination. Generally the specimens were taken from single ovaries and from ovaries which looked abnormal after total hysterectomy. Presence of pathologic lesions in the ovary as found in the different endometrial types are indicated below:

TABLE VII

Distribution of Nulliparous and Parous Patients with Normal Endometrium or Endometrial Hyperplasia in Different Age Groups

Age group years	Normal endometrium		Endometrial hyperplasia	
	Nulliparous	Parous	Nulliparous	Parous
20 or below ..	2	2	2	—
21-30	14	14	1	7
31-40	1	11	—	8
41-50	0	23	—	12

TABLE VIII

Endometrial Pattern in Relation to Ovarian Changes

	No. of ovaries with follic cysts	No. of ovaries with lutein cysts	Normal ovaries	Total no. of ovaries
Normal endomet. ..	3	4	3	10
Endomet. hyper- plasia	5	—	2	7
Total	8	4	5	17

It would appear from Table 7, that nulliparous patients were mostly in

It would appear from Table 8, that in about 30% of the 17 ovaries, with

normal and hyperplastic endometrium there was apparently no change. As indicated above, however, it is likely that in some cases tissues might have been taken from the wrong ovaries, and that lesions might have been present in the other ovaries. It would also appear from the above table that in 40% of the ovaries with lutein cysts, the endometrium was apparently normal, and that follicular cyst was present in the ovaries more frequently (70%) when the endometrium was hyperplastic than when it was normal (30%).

Comments

The objection to the conventional definition of dysfunctional uterine bleeding, i.e. bleeding in absence of pelvic pathology by ordinary clinical examination, relates to the term 'ordinary clinical examination'. According to this definition Sutherland found chronic endometritis, uterine polyp, endometrial tuberculosis and endometrial malignant disease in some of his cases. In addition, the authors found products of conception in one patient. Obviously one may expect to find other pathological lesions in similar investigations. Even routine biological tests for pregnancy may not exclude carneous mole and placental polyps. It is thus clear that the conventional definition leaves much room for personal bias. It is time that the condition is defined more precisely on the basis of histological examination as suggested by some workers.

The incidence of the main histologic types of dysfunctional uterine bleeding as encountered in the present investigation agrees with that of

Sutherland. However, a casual reference to the endometrial condition referred to earlier as the exaggerated oestrin phase may be necessary. It was obvious during examination of some slides that there were many more glands of the normal endometrium. Lewis has referred to a proliferative endometrium in the second phase of the menstrual cycle in absence of ovulation. The authors strongly felt that excessive secretion of oestrogen was responsible for excessive glandular activity which precedes transition to endometrial hyperplasia of the 'swiss cheese' type. There were six such cases of exaggerated oestrin phase and they have been grouped under 'apparently normal endometrium'. As indicated earlier, chronic endometritis was present in 7% of the cases of endometrial hyperplasia. Endometrial hyperplasia was mostly of the 'swiss cheese' type i.e. in 25 cases. In four cases the hyperplasia was of the polypoidal type. Besides, two cases were associated with endometriosis, and one with a very early stage of leiomyoma in the uterine wall.

A question may arise if there is some relation between the different types of endometrial changes. It was indicated earlier that the exaggerated oestrin phase may be a transitional stage of endometrial hyperplasia. It was also indicated that the graphic distribution of endometrial hyperplasia follows exactly the same configuration as that of normal endometrium. One would expect, therefore, that these two main types of endometrium, i.e. normal endometrium and endometrial hyperplasia, have the same pathogenesis. That

there is no correlation between the endometrial picture and the type of bleeding lends further support to this view. Bourne and Williams suggested cessation of hormones or failure of the endometrial receptors to respond to them. Thus it is likely that endometrial hyperplasia degenerates into endometrial atrophy. The relationship between irregular shedding or irregular ripening with other histological changes is not so clear. But it is likely that the different histological changes are inter-related.

This leads to the question of the importance of histopathological study. Lewis remarked that hormonal control of the uterine and endometrial blood vessels is probably more important than the endometrial pattern produced. Te Linde remarked that functional uterine bleeding can be present with such a wide variety of microscopic picture that it is obvious that bleeding is not inherently bound up aetiologically with the microscopic picture and that the actual mechanism of bleeding remains unknown. Novak and Novak, however, have recently suggested that there are many cogs in the menstrual machine, and functional derangements of more than one type may result in abnormal bleeding even with grossly normal pelvic organs. It is relevant to point out here that histopathological study in this disease was originally based on the hypothesis that change in the endometrial tissue and endometrial bleeding was related to the same process and that one is, at least in some way, the expression of the other. Under the present state of our knowledge about the histopathology of the disease, the authors are inclined to

agree with the remark of Traut and Kuder made 28 years ago that until more histopathological data are available, the time-honoured hypothesis has to be accepted. It may be suggested here that the standard of histopathological study in functional uterine bleeding has not yet attained the desired perfection and refinement.

A reference may be made to the possible association of emotional factor with functional uterine bleeding. Two facts emerging from the experimental data appear to be relevant: (1) In the majority (56%) of the cases the endometrium looked normal; and (2) 70% of the patients were about 25 years old, 85% of them having normal looking endometrium. Blaikley emphasized the importance of emotional or psychogenic factors in the causation of menorrhagia and suggested that their recognition will make surgery unnecessary in many cases. This remark may well apply to other forms of functional uterine haemorrhage. Here Bourne and Williams suggested two mechanisms of bleeding — (i) endocrinal and (ii) vascular. According to them the endocrine disturbance originates in the labile response of the anterior pituitary to stress of feeling. The vascular mechanism is likened to that which produces blushing or palor in nasal, gastric and other mucosae during fright, anger, etc. The authors suggested that the coiled arterioles of the endometrium react to emotional disturbance and their spasm results in necrosis, shedding and bleeding. The spasm of the vessels has been ascribed to endocrine influences or to the sympathetic nerve impulses controlling the vessels. It may be point-

ed out in this connection that economic difficulties, domestic trouble, marital unhappiness, fatigue, overwork etc. which form the background of emotional or psychological upset may be at least as important in our country, if not more, as in other countries.

As regards ovario-uterine relationship, we know that endometrium is often called the mirror of the ovarian function. In the absence of a reliable test for assessing the hormone level in patients, the histology of the endometrium has provided indirect evidence of hormone level in blood. Histological study of the ovary has been attempted to a limited extent. Only 17 ovarian tissue specimens were available to the authors and they found no change in 30% of them. With endometrial hyperplasia follicular cyst was associated in 30%. Lutein cysts were associated only with normal endometrium to the extent of about 25%. The association of cystic ovary suggests hormonal imbalance which is the aetiological basis of dysfunctional uterine haemorrhage, but it is apparent that this is only a vague suggestion of imbalance of the ovarian function. More detailed histological study of the ovarian tissue may have to be made.

A casual reference may be made to other aetiological factors suggested in literature. Blood dyscrasia has been suggested but its incidence, especially of the severe forms, is small. Accumulation of hormones in blood has been suggested in liver disease and in absence of liver protecting food like Vitamin B. These facts, however, cannot explain the

hard core of the problem. It will have to be accepted in the end that the aetiology of dysfunctional uterine haemorrhage is still elusive.

Summary

1. The incidence of dysfunctional uterine bleeding at the Hospital for Women, Patna, during the last five years was assessed from the hospital records. The average incidence during the period was 7.8%.

2. Hundred cases of dysfunctional uterine bleeding were investigated and histological examination of the uterine and ovarian tissues was made.

3. The disease was found to be maximum at about 25 and 45 years of age, being 22% and 25% respectively. The youngest patient was 18 years old and the oldest was 50.

4. Of the 100 patients, 20 were nulliparous and 80 parous patients.

5. The histological findings were: apparently normal endometrium 56%, endometrium hyperplasia 29%, chronic endometritis 10%, irregular shedding 3%, chorionic epithelioma 1%, and products of conception 1%. In all cases the coiled arterioles were found to be numerous and dilated near the surface.

6. The main types of bleeding were menorrhagia, polymenorrhoea and continuous or irregular bleeding. In most cases dysfunctional bleeding was not related to abortion or child birth. Menorrhagia was found in all cases of irregular shedding. The different types of bleeding were about equally distributed among cases of normal looking endometrium and endometrial hyperplasia which, therefore, appeared to have no parti-

cular affinity for any type of bleeding.

7. In the main histological types, the variations were: normal looking endometrium 52.6%, normal looking endometrium with exaggerated oestrin phase 6.3%, normal looking endometrium with chronic endometritis 7.4%, endometrial hyperplasia 24.2%, endometrial hyperplasia with chronic endometritis 3.2%, polypoidal endometrial hyperplasia 4.2%, endometrial hyperplasia with adenomyosis 1.0%, endometrial hyperplasia with leiomyoma in the uterine wall 1.0%.

8. Seventeen ovaries were examined histologically. In 30% of the ovaries associated with normal or hyperplastic endometrium, there was no apparent change. In 40% of the ovaries with lutein cysts the endometrium was apparently normal. It was further found that follicular cyst was present in the ovaries more frequently (about 70%) when the endometrium was hyperplastic than when it was normal (30%).

9. Comparatively more nulliparous patients were found to have normal looking endometrium. Out of 20 nulliparous patients, 17 had normal looking endometrium and 14 such patients were about 25 years old. On the other hand, out of 50 parous patients with normal looking endometrium, only 14 were about 25 years old. Higher incidence of cases near 25 years of age was mostly due to cases of sterility. It is suggested that a large incidence of functional uterine

bleeding near 25 years of age was due to emotional or psychogenic disturbance.

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