THE HORMONAL ORIGIN OF UTERINE FIBROIDS: AN HYPOTHESIS

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Uterine fibroids are the commonest of pelvic neoplasms and therefore should command the interest of all gynecologists. What is the source of these tumors is a question that is asked daily and one which can be answered only in generalities. In three former contributions (1, 2, 3) excessive stimulation of the myometrium by the ovarian follicular hormone has been suggested as a cause. That the action of this hormone is not specific for the endometrium, as demonstrated by the endometrial changes during the normal menstrual cycle, but that it affects the genital tract as a whole, is easily proved (4). When the action on the endometrium is abnormal, with resulting endometrial hyperplasia, there is an equally abnormal action upon the myometrium, which, if it is prolonged sufficiently, results in cellular metaplasia of the uterine muscle cell or cells, with the subsequent development of uterine fibroids.

According to Meyer (5), the histogenetic study of fibroids does not reveal any distinctive myoma mother cells in the uterine muscle from which a proliferating myoma might develop. He reports that the earliest appearance of a myoma is represented by a thickening of the uterine muscle bundles which are directly connected with the normal musculature of the uterus. De Snoo (6), on the other hand, claims that the uterus is a very primitive special organ which contains many undifferentiated cells, genitoblasts. During embryonic life these cells form the uterus proper, while in later life they provide the means of gestational hyperplasia and of regeneration of the endometrium during the puerperium. Under pathological conditions, due to ovarian hormonal dysfunction, these genitoblasts can give rise to the formation of uterine fibroids, endometriomas, or adenomyomas.

It is not the object of this paper to enter into a discussion of the primary source of the uterine fibroid, whether it be from myoma mother cells, as genitoblasts, or from cellular metaplasia of normal uterine muscle cells. The actual origin of the fibroid is unimportant; the paramount question is the determination of the exciting factor which controls the cellular change or which stimulates the genitoblasts to tumor proliferation. The hypothesis is here set forth that this exciting cause has its origin in excessive stimulation on the uterine muscle tissue by the ovarian follicular hormone.

Graves (7) has aptly observed that uterine fibroids possess certain attributes that seem to place them in a borderland between physiologic hypertrophy and true neoplastic growths. "Their great frequency
(20 per cent of all women over 35), their apparent coincidence with the sexual era, their regression after ablation of ovarian function, their histological similarity to diffuse hypertrophy and gestational hyperplasia, and their structural identity with the normal uterine musculature, are all familiar facts that lend to these tumors a physiologic glamour which they probably do not deserve."

There are several popular theories of the etiology of uterine fibroids.

(1) Irritation Theory: The irritating stimulus of infection activates abnormal uterine growth. In the Negro race especially, pelvic infection is so universally associated with uterine fibroids that it is difficult to determine which is the cause and which the result.

(2) Circulatory Theory: Polak and Mazzola (8), in experimental torsion of the vessels around the uterus, parametrium, and contiguous tissues, found marked hyperplasia and hypertrophy of all uterine layers, but no fibroid formation.

(3) Growth-energy Theory: Differing from all other organs, the uterus does not undergo atrophic changes while not functioning. When pregnancy intervenes, it takes on an entirely new rôle, developing by hypertrophic and hyperplastic changes into an organ many times larger than its normally mature size. When pregnancy does not intervene, the growth-energy theory assumes an unsatisfied development with the formation of fibroids.

(4) Sterility: Patients with fibroids exhibit sterility three to four times as frequently as normal women. Whether sterility is the cause of the fibroids or the fibroids the cause of the sterility is the essential problem.

(5) Heredity: Occasionally fibroids are found in sisters or in mother and daughter, although only 21 women in Lynch's series of 683 cases gave a suggestive family history.

(6) Race: Fibroids are present about 9 times as frequently in the colored race as in the white.

The present tendency is to seek the cause of uterine fibroids in some irregularity of function of the anterior pituitary and ovarian hormones, which regulate the growth and function of all the pelvic organs. That the entire genital tract is stimulated to hypertrophy and hyperplasia by this sexual growth factor has already been suggested (4). When this stimulation is abnormal, as in the presence of excessive secretion, all forms of overgrowth of the uterine endometrium and musculature result. Endometrial hyperplasia, the result of the unopposed and persistent action of the estrogenic principle (9, 10, 11), is a manifestation of this dysfunction in only one locality. The myometrium, the tubes, aberrant endometrium, the breasts, or, indeed, any part of the genital tract may likewise show abnormal growth from this stimulation.

A distinction should be made between uterine hypertrophy and hyperplasia and true fibroid formation. In hypertrophy the etiological factor is an abnormally high concentration of the estrogenic principle in the circulation, acting apparently on normal uterine muscular tissue. In true tumor formation, on the other hand, as in fibroids, the increased ovarian follicular hormone in the blood is acting upon a hypersusceptible tissue which has the capacity to concentrate this hormone at the site of the tumor. That such concentration does occur has been demonstrated by Lewis and Geschickter (12), who have shown the presence of definite amounts of the gonadotropic and the estrogenic principles in a uterine fibroid.

In the three contributions referred to above (1, 2, 3), the hypothesis was offered that excessive ovarian hormone stimulation resulted in im-
mediate endometrial hyperplasia, since such endometrial conversion takes place rapidly, and in eventual myometrial changes in the nature of fibromyomatous growth, provided the stimulation is prolonged. This hypothesis has found recent support in King's investigations (13). He notes the frequency of association of endometrial hyperplasia and uterine fibroids, a frequency sufficiently high to exclude a mere chance relationship. Of 114 cases of fibroids, 71 per cent exhibited endometrial hyperplasia. A further suggestive point is found in the frequent combination of endometrial and myometrial hyperplasia. Allen (14) also supports the hormonal origin of uterine fibroids. To him the frequent association of fibroids with endometrial hyperplasia suggests that they, like the latter, should be looked upon as an end-result of hormonal cell stimulation, another type of cellular metaplasia caused by underlying glandular dysfunction. Such a postulate, if accepted as a starting point, will lead into the field of benign tumor etiology in general, while further metaplasia or dedifferentiation carries on directly into the realm of malignancy.

The present paper offers two years' additional clinical evidence in support of a cause and effect relationship between multiple follicle cysts of the ovary, with excess estrogenic hormone secretion, and immediate production of endometrial hyperplasia and more latent development of uterine fibroids, provided the stimulation is sufficiently prolonged.

Forty-four cases of endometrial hyperplasia were studied. On each patient a curettage was performed and the diagnosis made microscopically. In no case, either by bimanual examination or with the curette, was a uterine fibroid observed. In addition, in 20 of the cases (45 per cent) a laparotomy was performed for other reasons. In no instance was a fibroid found, but multiple follicle cysts of the ovaries were observed in every case. After varying intervals, an average of four years and nine months, all 44 patients returned for a second operation, this time for multiple uterine fibroids. The histological findings in the endometrium, myometrium, and ovaries are offered as evidence of an interrelationship between the multiple follicle cysts of the ovaries, endometrial hyperplasia, and uterine fibroids (Table I).

Analysis of Table I: In every instance the uterus was removed because of uterine fibroids. The myometrium exhibited hyperplasia in 24 cases, or 55 per cent. The endometrium also was hyperplastic in 40 cases. Multiple follicle cysts of the ovaries were present in every instance, while mature corpora lutea were found in 4 cases, associated with promenstrual endometrium. Unless both ovaries or the total ovarian tissue are studied in their entirety, it is unwise to draw conclusions concerning the presence or absence of corpora lutea, since their absence is so closely related to endometrial hyperplasia. On the other hand, any explanation for the co-existence of multiple follicle cysts of the ovaries and corpora lutea must be in the nature of an hypothesis. That endometrial hyperplasia is only infrequently a permanent condition is seen in girls at puberty, in whom irregularities of menstruation
spontaneously change over into a normal rhythmical cadence. During this conversion the existence of multiple follicle cysts and corpora lutea may be observed.

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<th>Table I</th>
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<tr>
<td><strong>Type of operation</strong></td>
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<tr>
<td>Hysterectomy</td>
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<td>Bilateral salpingo-oophorectomy</td>
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<tr>
<td>Removal of all remaining ovarian tissue</td>
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<tr>
<td>Unilateral salpingo-oophorectomy</td>
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<td>* All ovarian tissue removed in 28 cases, 64 per cent of total.</td>
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**Condition of myometrium**
- Fibromyomatous: 44 cases
- Hyperplastic: 24 cases
- Fibrotic: 6 cases
- Adenomyomatous: 8 cases
- Normal: 14 cases

**Condition of endometrium (microscopic)**
- Hyperplastic: 40 cases
- Premenstrual: 4 cases

**Condition of ovaries (microscopic)**
- Multiple follicle cysts: 44 cases
- Corpora lutea: 4 cases

**Miscellaneous**
- Salpingitis and adhesions: 38 cases
- Ovarian endometrial transplants: 22†
  † 50% of total.

Ovarian endometrial transplants were present in 22 cases, or 50 per cent. If to this are added the 8 cases of adenomyomas, endometriomas were observed in 64 per cent of the series, since 2 cases exhibited combined myometrial and ovarian endometrioma.

These 44 cases of endometrial hyperplasia, in which a second operation was performed on an average of four years and nine months later for uterine fibroids, are convincing evidence that the prolonged and unopposed action of the estrogenic principle on the uterine endometrium and myometrium results (1) in immediate endometrial hyperplasia, and, if stimulation is prolonged sufficiently, (2) in uterine fibroids.

**Associated Conditions:** That the genital tract as a whole, and also the mammary glands, are under the influence of the estrogenic principle has already been suggested. Aberrant endometrium is also under the control of this hormonal principle. Since the morphological and functional characteristics of endometriomas and uterine endometrium are similar, and since excess ovarian hormone stimulation is the cause of endometrial hyperplasia, it is logical to conclude that the initiating factor of endometriomas is also the estrogenic principle. Whether the primary source of the endometrioma is from implantation of living endometrial grafts or from cellular metaplasia of the serosal or germinal mesothelium is unimportant; the all-important fact is that the stimulation of these implants to neoplastic proliferation or the cellular metaplasia phenomenon is controlled by the estrogenic principle.

Geschickter and Lewis (15) have gone a step further and have described the action of the estrogenic principle on the mammary glands.
Their observations seem to warrant the conclusion that gynecomastia in the male, and virginal hypertrophy and fibro-adenoma formation in the female breast, are dependent upon pathological variations in the action of the ovarian follicular hormone upon the duct epithelium. Prolonged and interrupted stimulation by the estrogenic principle, just as in uterine fibroid formation, rather than brief high concentration, is necessary for the production of these mammary conditions.

Conclusions

Pathological and clinical evidence is offered to support a hypothesis that there exists a cause and effect relationship between the unopposed and persistent action of the estrogenic principle, produced by multiple follicle cysts of the ovaries, on the uterine endometrium and myometrium, and the production of (1) immediate endometrial hyperplasia and, provided the stimulation is sufficiently prolonged, (2) more latent uterine fibroids. Since this estrogenic principle affects the genital tract as a whole and also controls the development of the mammary glands, it would appear that this same hormonal stimulation is the initiating factor in the production of endometriomas and fibro-adenomas of the breast.

Bibliography