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ABSTRACT - From 1861 to 1962, clinicopathologic research tried to explain the association of abnormal uterine bleeding with uterine enlargement. The etiology

was theorized as metropathy, suggesting that myometrial dysfunction may predispose to abnormal uterine bleeding. Research reached a nadir in 1962, when a major review dismissed myometrial hypertrophy as a plausible explanationafter prior rejections of the theories of chronic myometritis, fibrosis uteri, and subinvolution as causes of bleeding. Subsequent to this arose a crusade against unnecessary hysterectomies in the 1970's. Although myometrial hyperplasia (MMH) was proposed in 1868, it is only in the last 25 years that tangible evidence has supported that idea. It now appears that clinically enlarged uteri are due to globoid outward bulging of the uterus, caused by increased intramural pressure; often unrelated to either uterine weight or myometrial thickness. Abnormal (dysfunctional) uterine bleeding may often be due to spontaneous rupture of thrombosed dilated endometrial vessels, due to the combined effects of obstructed venous drainage by increased intramural pressure, and Virchow's Triad. Despite a century old known association of parity with naturally occurring outer wall myometrial scars (fibrosis uteri with elastosis), it was not previously suggested that these may reflect healing reactions to muscle tears during labor and delivery. We now suggest that smaller, similar inner wall elastotic scars in the nerve rich inner myometrium may explain many cases of pelvic pain. This review suggests that diverse pressure-related lesions may be present in clinically abnormal uteri that have been called "normal" since the crusade against unnecessary hysterectomy.

Key words: Hysterectomy, uterus, abnormal uterine bleeding, chronic pelvic pain

Unnecessary Hysterectomy

Leading biomedical researchers have recently asked a profound and disturbing question: What happens when underperforming big ideas in research become entrenched?"(1). A primary goal of this article is to suggest that "unnecessary hysterectomy" may be an "underperforming big idea that has become entrenched". We suggest that most symptomatic clinically abnormal uteri signed out by pathologists as normal using standard textbook criteria are probably abnormal. Ever since the crusade against unnecessary hysterectomies escalated in the 1970's (2-5), it has been difficult - if not impossible - for a pathologist to diagnose a uterine abnormality not cited in standard pathology textbooks; without being suspected of supporting the practice of unnecessary hysterectomy, and/or of making scientifically unsubstantiated interpretations. Some pathologists even declined to report the presence of seedling myomas (< 1 cm), for fear that such a report might be misconstrued as justifying the operation (6).

The crusade against unnecessary hysterectomy did not take into consideration the fact that pathologists and gynecologists had been working together for over 100 years to try to understand the association of clinically enlarged uteri with abnormal uterine bleeding (7-9). Collaborative research in this area, with rare exceptions, came to a virtual standstill. The fact that pathologists could not identify a textbook abnormality does not mean those clinically abnormal uteri were histologically normal. Histology textbooks do not recognize myometrial hyperplasia (MMH) (10) as normal. MMH is defined by high cellularity with high N/C ratio; while myocyte hypertrophy conversely refers to enlarged muscle cells

with lower cellularity and low N/C ratios (as occurs during pregnancy and in response to progesterone treatment). The closely related term myometrial hypertrophy eventually came to be defined primarily on the basis of uterine weight, without regard to routine microscopy on H&E stains.

Many gynecologists were taught to tell patients that "the pathologist found nothing wrong with the uterus", so the reasons for pain and bleeding were probably hormonal alterations or uterine infections. Even with the advent of new technologies such as laparoscopic and robotic surgery, the fundamental understanding of non-neoplastic uterine diseases was somewhat frozen in time.

In the 1990s, a collaboration was begun at Rochester General Hospital to re-evaluate hysterectomies that had been performed for pain or uterine bleeding, in which the pathologist signed out the case as " no significant pathology", and referred the case for review at Tissue Committee. All 41 hysterectomies reviewed at Tissue Committee 1991-98 had been considered justified, as all women had received a thorough diagnostic evaluation, and had been treated with appropriate medical therapy. On retrospective chart review, all cases met ACOG criteria published in 1998 (5). The cases were retrospectively scrutinized for MMH, which had been described grossly and microscopically, and analyzed morphometrically, in 1995 (and independently confirmed under the alternative terminology of junctional zone myometrium) (10,11). Case reviews noted other causes for hysterectomy in 7 patients, and in 1 case the medical records could not be located. These 8 cases were dropped, leaving 33 hysterectomies for unexplained dysmenorrhea, chronic pelvic pain, and/or abnormal bleeding (12). Note was made of uterine size on physical

examination and, if available, ultrasound. The pathology reports were checked for uterine weight and myometrial thickness. The pathology slides were systematically photographed. Increased cellularity and nucleus/cell (N/C) ratio, compared to normal myometrium in the same uterus, were used to identify MMH in the photographs (10). Obvious photos not needing morphometry were called MMH.

All 33 possible "unnecessary hysterectomies" had microscopic evidence of MMH (10,12), and clinically enlarged uteri were shown to correlate with outward bulges caused by MMH. In 1999, preliminary findings were presented at an NIH Symposium (12). Despite the fact that 33 otherwise unexplained hysterectomies for dysmenorrhea, chronic pelvic pain, and/or abnormal bleeding had all been signed out as normal uteri by textbook criteria; there had been no unnecessary hysterectomies at a university-affiliated community hospital 1991-98, according to ACOG clinical criteria. It was not possible to get this information published at that time.

It may or may not be a coincidence that despite additional publications on MMH (13-17), it is still not a standard textbook diagnosis. We believe that many clinically abnormal uteri continue to be signed out as normal, most of which probably have clinically significant MMH (10,17). This paper will demonstrate obvious gross findings in MMH, presented at another NIH symposium in 2010 (18), which correlate with detection of clinically enlarged uteri on physical exam. Gross photographs of hysterectomies also correlate with inner wall bulges on pelvic ultrasound that are commonly misinterpreted as leiomyomata (17). It was recently suggested that inframucosal MMH may not only explain inframucosal bulges on

ultrasound, but also" thickened endometrial stripes" in cases with thin endometrium on histologic exam (17).

Supportive immunohistochemical studies of MMH were presented at an NIH symposium in 2005,, and are partly incorporated into the present work (19). We believe it may now be time for the pendulum to swing back in the other direction, permitting pathologists to offer possible explanations for pelvic pain and abnormal bleeding, subject to the clinical judgment of the gynecologist.

What is a Normal Uterus?

In their study of myometrial hypertrophy, Lewis et al encountered serious difficulties with defining the size of a normal uterus (8). They had defined myometrial hypertrophy purely on the basis of uterine size >120 grams, stating that the histology looked the same in both the myometrial hypertrophy group, and the group of "normal" uteri that weighed 115 grams or less. The problem may be best understood by contrasting the clinical view of a normal uterus with the viewpoint of pathologists. This point is emphasized because, historically, pathologists have been criticized for reporting various findings without "normal controls".

It may be obvious to most gynecologists that a clinically normal uterus is one that causes no symptoms or abnormal radiologic findings, is normal on physical examination, is associated with normal menstrual periods, can support normal deliveries of normal babies, and undergoes normal involution after a normal menopause. It is much less clear what constitutes a normal uterus on examination in the laboratory, where the pathologist's perspective dictates the final diagnosis. The

vast majority of women with clinically normal uteri never have a hysterectomy, and pathologists may never get to systematically scrutinize such uteri. There are only 3 ways for a pathologist to have an opportunity to examine a clinically normal uterus, and all 3 pose significant obstacles to systematic analysis.

The first way is for a hysterectomy to be performed incidentally, perhaps in the course of surgery for an ovarian neoplasm. In such cases, the primary concern of the surgeon, the pathologist, and the patient is the ovarian tumor. The pathologist generally gets little or no information about the myometrium in such cases, and generally pays relatively little attention to the myometrium - unless there is some obvious uterine pathology. Although the pathologist may have just examined a clinically normal uterus, this cannot be stated with certainty since no detailed clinical history pertaining to the uterus was given. Uteri removed for prolapse also fit this category. As in all hysterectomies, there are known risk factors for prolapse, which make this a selected group of uteri; and no history as to whether the prolapsed uterus had always been clinically normal is generally given.

The second way is for the uterus to be examined in a medical autopsy, whose primary purpose is to establish the cause of death. Hospital autopsies by general pathologists are even more restricted in regard to uterine examination than incidental hysterectomies or prolapsed uteri. The uterus generally has nothing to do with the cause of death; the clinician generally gives little or no history about the uterus; and expresses little or no interest in the uterine findings. Furthermore, tissues may be somewhat autolysed. Most of these cases are in older patients of internists, usually postmenopausal. With the declining autopsy rate in most

hospitals due to lack of reimbursement and lack of regulatory requirement, this deficiency is unlikely to ever be remedied.

The third way is for a forensic pathologist to examine the uterus of a victim of accidental death, suicide, or homicide. This population may tend to be enriched for premenopausal women, but once again the focus is not on the uterus - which is usually irrelevant to the cause of death. In most forensic cases, there is no gynecologic history, and the examination of the uterus is so cursory that histologic examination may be considered unnecessary. Again, the pathologist may have just examined a clinically normal uterus, but cannot know this with certainty.

The bottom line is that - to date - no pathologist can claim to have meticulously scrutinized the myometrium of a series of asymptomatic clinically normal uteri. Even Schwalm and Dubrauszky, who did a meticulous morphometric study of uteri (20) - some surgically obtained, some from cadavers, and some from pregnant women - did not state the specific indication for most of their hysterectomies.. We suggest it may be unrealistic to expect a case control study with "age matched normal uteri", for truly rigorous scientific comparison of "normal myometrium" to any purported myometrial abnormality. The best one can do is to use areas of "normal myometrium" in a given uterus, to compare and contrast with structural variations elsewhere in the same uterus (10-12,14-19,21).

In 1970, Langlois addressed the concern about defining the size of the normal uterus (22).He examined 1348 hysterectomies. He found that nulligravid uterine weight was 60-70 grams at age 30 to 50; with 45-60 grams at younger and older ages. Pregnancy aborting prior to fetal viability did not seem to affect uterine

weight. This important observation reflected that most uterine growth occurs in the 3rd trimester. After one child was born, uteri averaged in the 80-100 grams range, falling to < 60 grams after age 60. After 2-3 children, uteri averaged 100-120 grams, again falling to < 60 grams after age 60. After 4-5 children, uteri averaged 120-140 grams, falling to 80-90 grams after age 50, and to 70-80 gm after age 60. After 6 or more children, uteri were generally > 120 grams, but fell to 100-110 grams after age 50.

"Normal" uterine weight also varied with age, increasing from around 56 grams in teenagers, to 100-120 grams at age 20-49; falling to about 84 grams after age 50, and to 56 grams after 60 years. Race was also a factor, at least in nulligravid uteri - with a Caucasian average of 49 grams, and an African-American average of 73 grams. After one baby had been born, the difference disappeared, with both races averaging 90 grams in uterine weight.

We believe these data suggest that the 120 gram benchmark used by Lewis et al (8) to debunk myometrial hypertrophy as a clinical entity was invalid. Although uterine weight had become clinically irrelevant by 1970, pathologists using the 120 gram criterion for abnormal uterine enlargement (myometrial hypertrophy) were no longer able to make this diagnosis without knowing a woman's age and parity. Langlois acknowledged that uteri > 250 grams were "probably abnormal", and felt that further study in this area was needed. Although Langlois did not believe in a clinical diagnosis of either myometrial hypertrophy or uterine subinvolution (17,22), the effect of subinvolution on his data may have been profound. Careful

reading of that paper reveals extremely broad standard deviations. Clearly, some uteri shrank back postpartum a lot more than others.

In 1979, Honore studied the association of abnormal bleeding and uterine enlargement with the intrauterine contraceptive device (23). He emphasized symmetrical globular enlargement, with a weight > 125 grams, to define myometrial hypertrophy; acknowledging that it was not a clinical entity at that time. Although our current experience is at odds with Honore's weight criterion, our observations tend to confirm his observation that a symmetrical globoid bulging uterus is a pathologic correlate of a clinically enlarged uterus (**Figures 1a,b**). Twelve of 14 uteri (86%) removed for IUD-associated menorrhagia fit Honore's criteria for myometrial hypertrophy. Honore's control group consisted of 254 enlarged uteri, in women aged 26 to 54, with no IUD. In his control uteri, uterine enlargement was mostly due to fibroids or adenomyosis, with myometrial hypertrophy representing only a small fraction. He reported that thickness in myometrial hypertrophy was often > 2 cm. Most importantly, in our view, Honore noted that localized subserosal or submucosal myometrial thickenings could be observed. This was later confirmed by us in uteri with grossly obvious MMH, where we documented both subserosal ridges and inframucosal bulges (**Figure 1c**) (10,17). For Honore, myometrial hypertrophy was more likely (about 60%) when uteri weighed 125-150 grams. In our experience, globoid bulging uteri with clinically significant MMH (**Figures 1a,b**) can have normal uterine weights by Langlois' age/parity criteria (22). Honore concluded : "It is conceivable, though unproven, that an abnormal … myometrium is unable to promote adequate hemostasis during menstruation".

Nonetheless, in 1980, a major authoritative gynecologic pathology monograph stated that myometrial hypertrophy was a "dubious entity" that could only be diagnosed if one knew the patient's age and parity, and took the possibility of hormonal therapy into account (24). A pathologic diagnosis of myometrial hypertrophy by modern criteria requires a weight of 201 g for parous (1-3) uteri, or 130 g for nulliparous uteri (25).

We suggest two possible mechanisms for idiopathic myometrial hypertrophy: 1) long term treatment with progesterone, leading to diffuse myocyte hypertrophy (**Figure 1d**); and 2) failure of postpartum apoptosis to completely reverse gestational myocyte hyperplasia; so that postpartum uteri fail to return to baseline size, i.e., true subinvolution (17). It must be kept in mind that the low N/C ratio of myocyte hypertrophy (**Figure 1d**) is the opposite of the high N/C ratio in MMH (10,17). It must also be kept in mind that the diagnosis of idiopathic myometrial hypertrophy is based on weight alone, regardless of microscopy (25); and that gestational myocyte hyperplasia cannot be recognized under the microscope due to concurrent gestational myocyte hypertrophy. Dealing with these complexities has long hindered progress in this area.

What causes abnormal uterine bleeding in a clinically enlarged uterus?

From 1861 to 1962,, many ideas were proposed to explain how an enlarged uterus might cause abnormal bleeding (7,8). Today, the question remains: “What causes abnormal bleeding in a clinically enlarged uterus when the endometrium is

normal proliferative, secretory, or inactive; and there does not seem to be a hormonal explanation, tumor, adenomyosis, or infection?"

The first major idea was that chronically inflamed myometrium (chronic metritis), might lead to endstage induration and fibrosis (7). By analogy with postpartum uterine atony as a cause of life-threatening hemorrhage, the basic premise was that normal myometrial function was required to help control abnormal uterine bleeding. This theory of "metropathy" can still be found in modern textbooks and literature. It has never been either proven or disproven.

As an incidental microscopic finding, chronic myometritis can be associated with myofiber disarray (21) (**Figure 1e**), so it is plausible that it could disrupt myometrial function. However, in our experience, mild chronic myometritis is not usually associated with extensive myometrial scarring, and is unrelated to histories of abnormal bleeding in clinically enlarged uteri. A more exuberant form we label as eosinophilic myometritis (**Figure 1f**), with focal loss of muscle tissue, can be seen after ablations or endomyometrial resections; which do induce scars and can be associated with continued abnormal bleeding (21). In 1940, it was suggested that chronic myometritis may be clinically significant in cases of tuberculous endometritis and pelvic inflammatory disease, and this still seems credible (8,26).

In 1868 Finn posited that both uterine enlargement and myometrial dysfunction might be due to **MMH** (increased number of myometrial cells) (27). He presented no convincing data to support this theory, which had no advocates in the succeeding century. However, recent observations tend to support Finn's idea (see below). In 1897, Reinicke ascribed the abnormal bleeding to vascular changes that

are still conspicuous in modern hysterectomies (i.e., arteriosclerosis) (28) (**Figure 2a**), but this theory failed to gain long term support (8).

The theory of fibrosis uteri (in the outer wall) came to the fore in 1902, with most believing this was due to chronic myometritis (29-31) (**Figure 2a**). Some thought that chronic irritation led to an increase in muscle tissue, along with fibrosis (31); while others thought that an increase in muscle and/or fibrous tissue due to multiparity may have led to the bleeding (32,33). It was suggested in 1914 that an increase in elastic tissue in multiparous uteri might be the major cause of otherwise unexplained abnormal bleeding (34). In 1933, fibrosis uteri was scrutinized in a study of 40 autopsy uteri and 19 hysterectomies (35). Ages ranged from 17 to 88. Most were nulliparous uteri with no history of uterine bleeding. Deaths were due to accidents, acute infections, and chronic disease. 15 patients had a history of abnormal bleeding. It was emphasized that parous uteri had a striking increase in elastic tissue – an observation which dated back to 1903, and which was considered a part of the general knowledge of all pathologists up through the 1970's (36). However, elastosis in parous uteri was no greater in those with abnormal bleeding; and fibrosis increased with age; suggesting that fibrosis uteri did not cause abnormal uterine bleeding. Despite the clear association with parity, it seems that no consideration was given to the possibility that these naturally occurring outer wall scars might be due to tears in outer wall muscle during labor and delivery.

In 1940, review of a large series of hysterectomies endorsed the diagnosis of chronic subinvolution (26). Purported histologic evidence of subinvolution was residual unabsorbed elastic tissue around thick-walled arteries and veins deep in

the uterine wall (**Figure 2a**). In that review, chronic metritis secondary to chronic endometritis was reported; and myometrial hypertrophy (due to a need for excess contractions of the myometrium) was diagnosed in patients with endometrial hyperplasia.

From 1944 to 1949, 3 studies debated the relative significance of myometrial hypertrophy vs. fibrosis uteri in causing uterine enlargement with abnormal bleeding (37-39). The criteria for chronic subinvolution described in 1940 (26) were not endorsed by these or any other subsequent studies, some of which related myometrial hypertrophy to hormonal influences such as prolonged estrogen administration (8).

Dramatic uterine enlargement >250 grams with hypertrophic myocytes with a low N/C ratio (the opposite of MMH) has been seen by us after long term Depo-medroxyprogesterone acetate (**Figure 1d**), and leuprolide has the opposite effect (17). The levonorgestrel releasing IUD was noted anecdotally to have a unique effect. As compared to the usual finding of hypercellular inner myometrium with scant collagen (10,17,21), one could label this pattern as an inner wall variant of fibrosis uteri (**Figure 2b**). There is no evidence at this time that these diverse hormonal effects are functionally significant "metropathies". More study is needed.

In 1962 Lewis et al did a meticulous review, testing the hypothesis that myometrial hypertrophy was a clinicopathologic entity responsible for both enlarged uteri and abnormal bleeding (8). They chose 120 grams as the borderline between 57 uteri with no tumor or inflammation**;** and 56 uteri weighing 115 grams or less, also with no tumor or inflammation. Their raw data confirmed the notion

that some uteri involute after pregnancy, while others do not (which we feel is the proper definition of subinvolution) (17). Although their data suggested that larger uteri are associated with more pregnancies, and with a tendency to fail to return to the size of nulligravid uteri; they did not endorse the diagnosis of subinvolution. They noted prominent vessels in uteri > 120 grams, but gave no serious consideration to the vascular theory of Reinicke (28). Routine microscopy was reportedly the same in both groups. Their morphometry suggested larger muscle cells in the heavier uteri; but they did not control for location of the measured muscle cells. Today it is appreciated that outer wall muscle cells tend to be larger, with a lower N/C ratio (10,11 ,14,16,17,21).

Furthermore, there was a significant difference in age, with 28% of smaller uteri in women 50-69; while only 5% of larger uteri were in women 50-69. This suggests that their smaller uteri may have had smaller muscle cells due to age-related postmenopausal cell shrinkage (10,17). The most important finding, of this study was that only 19% of uteri > 120 grams were clinically enlarged on physical examination; while only 58% of clinically enlarged uteri weighed > 120 grams. This fits with our current experience, which suggests that a globoid bulging uterus (**Figure 1a,b**), as per Honore (23), is responsible for the recognition of a clinically enlarged uterus, regardless of uterine weight. After this review, clinicopatholgogic research in this area reached a nadir; predisposing to the crusade against unnecessary hysterectomies. (2,3).

SOME NEW ANSWERS

Increased Intramural Pressure

An important concept - not adequately considered in the century of research (1861-1962) on chronic metritis, fibrosis uteri, subinvolution, and myometrial hypertrophy - is that the uterus is frequently subject to increased intramural pressure - with histologically apparent pressure effects. These include congestion, vascular ectasia (both veins and lymphatics) and interstitial edema of the outer myometrium (17,40)(**Figures 1b,2c,d,e**)**.** These pressure effects are most conspicuous in fibroid uteri, where vascular ectasia in the endometrium is caused by obstruction of venous drainage. This presumably explains why and how myomas can lead to abnormal bleeding (**Figure 3a**) (41). Although this important discovery by Farrer-Brown et al in 1971 is cited in gynecology texts, to explain to patients with fibroid uteri why they needed a hysterectomy for abnormal bleeding; it appears to be unknown to many pathologists.

Even more important, and equally unfamiliar to most pathologists, these dilated fragile endometrial vessels were seen by Baggish et al in 1989 to rupture spontaneously during hysteroscopy in uteri with submucous fibroids, leaving behind endometrial ecchymoses (42). This explanation for abnormal bleeding was generated in the era when "an underperforming big idea had become entrenched", i.e. "unnecessary hysterectomy" (1,4). It provided a plausible long-sought explanation for what Silverberg described in 1977 as dysfunctional uterine bleeding (43). Modern gynecology textbooks continue to note that endometrial biopsies for abnormal uterine bleeding frequently manifest normal proliferative or secretory endometrium (44).

In 2012, we did an unpublished prospective study of 100 biopsies and curettages to see if the grade (size) or stage (extent) of dilated endometrial vessels predicted subsequent hysterectomy for abnormal bleeding a year later. It did not. Our current working hypothesis is that such vessels rupture and bleed only when they thrombose. Virchow's triad of slow flow, pressure-induced endothelial injury, and hypercoagulability may apply in this scenario. Tissue Factor of the extrinsic pathway should be explored as the possible mechanism for hypercoagulability, since blocked venous drainage may cause tissue injury by means of chronic exposure to venous hypoxia. We have noticed that the extravascular fibrin thrombi seen in biopsies with breakdown of otherwise normal proliferative or secretory endometrium tend to be the same size and shape as intravascular thrombi in such biopsies. This same mechanism may be operative when venous thrombosis induces hemorrhage and necrosis in benign endometrial polyps, which have a less delicate stromal component than normal proliferative or secretory endometrium.

Gross inward and outward bulging (**Figures 1a,b,c**), and microscopic pressure effects, comparable in degree to pressure effects seen in many fibroid uteri, can be seen in uteri that lack significant fibroids (10,17). In our experience, increased intramural pressure in nonfibroid uteri is most often due to MMH, first hypothesized by Finn in 1868 (10,17,27,40) (**Figure 3b**). Bulky adenomyosis that is grossly visible can do the same thing, as baseline myometrial tone has to accommodate an increased amount of intramural tissue (23,45). In our experience, when adenomyosis is focal, superficial, and microscopic, the pressure effects are generally due to concurrent bulky MMH (17). More study is needed in this area, and

will require systematic gross photographs taken after 48 hours of formalin fixation (10,17) (**Figures 1b, 3c**). New slices tend to yield the best photographs.

MMH, like fibroids, can also lead to inner wall vascular ectasia (**Figure 3d**), which contrasts with the usual slitlike pattern of inner wall vessels (**Figure 3e**), as compared to outer wall vessels (**Figure 3f)**. Inner wall vessels are usually slitlike (**Figure 3e**) due to increased intramural pressure in the midst of hypercellular, grossly firm MMH (**Figures 3b,3c**). Inner myometrial vascular ectasia often seems to be due to deflection of increased pressure inwards, by subserosal ridges which resist outward distension (10,17,23)(**Figure 1c)**. Ablations may fail to alter these pressure effects, so inner myometrial vascular ectasia (**Figure 3d**) may persist in postablation scars that extend to the surface (once endometrium is gone), causing continued postablation bleeding. These surface scars may manifest hemosiderosis as proof that they were bleeding postablation scars.

Clinically Enlarged Uteri

Recent observations tend to confirm Honore's suggestion that the pathologic basis for clinically enlarged uteri is a globoid bulging uterus (**Figure 1a,b**)(18, 23). Amongst uteri under 200 grams, correlation of clinical enlargement with uterine weight has been effectively discredited (8). In our unpublished study of hysterectomies referred to Tissue Committee, we found that clinical enlargement was related to outward bulging caused by MMH (**Figure 1b**), but not to myometrial thickness (10,12,17). This is apparently because increased myometrial thickness can be due to pressure-induced inward bulges (**Figure 1c**), sometimes observable on pelvic ultrasound (17) but not detectable by palpating the outer contour of the

uterus. These globoid bulging uteri commonly have both outer pressure effects (**Figures 1b,2d,e)** and endometrial vascular ectasia (**Figure 3a**); thereby providing a possible explanation for the century old association of clinically enlarged uteri with abnormal uterine bleeding (7,8,17).

Although clinically significant inframucosal MMH can be striking on gross examination **(Figures 1b, 3c**); it can be easily missed in routine practice (10,17). Pale firm bulging MMH is best seen after thorough formalin fixation; requiring re-examination of the gross specimen after microscopic review of the slides. Paleness may not be apparent in fresh or partly fixed uteri, processed within 24 hours of specimen arrival (**Figure 1c)**; even when the lesion was detected sonographically, caused a clinically enlarged (bulky) uterus on physical examination and/or ultrasound, and was firm to palpation (a technique not routinely applied by all pathologists) (17). Paleness can also be inconspicuous in uteri of excessive weight, even if they do not meet modern criteria for diagnosing idiopathic myometrial hypertrophy (17,22,23,25). Some of the cases with pale, firm bulging MMH may also have seedling myomas (<1cm) or foci of microscopic adenomyosis – neither of which is bulky enough to account for outward bulging and pressure effects.

True Subinvolution, Senescence, Regression, and Metropathy

We now have a better understanding of subinvolution of the uterus. Schwartz interpreted globular elastosis around thick-walled outer vessels as evidence of subinvolution (26) (**Figure 2a**); but today it is understood that uterine enlargement during pregnancy involves both gestational hypertrophy of myocytes, and gestational hyperplasia of myocytes. Postpartum, some muscle cells gradually

shrink back to antepartum size, while others undergo apoptosis (**Figure 4a)**, thereby reducing cell number (46-48). Involution of gestational myocyte hyperplasia must be highly variable, since some multiparous women end up with very large uteri, over 200 grams; while others involute back to the same size as nulliparous uteri (8,22). Much remains to be learned about the biologic basis for this variability, but it is clear that subinvolution - defined in terms of uterine size as a function of age and parity, truly exists.

Rapid postpartum involution of gestational myocyte hyperplasia due to apoptosis is very different from the process of senescence, which occurs in normal myometrium of elderly women, but is more commonly observed in MMH in hysterectomies for pain and/or bleeding (10,16,19). Actively growing MMH has increased N/C ratio, nuclear size, and cellularity, most pronounced at the growth zone under the endomyometrial junction (EMJ) (10,14,17). These nuclear features are best appreciated with immunostains for estrogen receptors (and progesterone receptors) (19) (**Figure 4b,c,d)**. Using a morphometric method that multiplies grade of intensity (3) by proportion of muscle cell nuclei stained (about 100), we have found that the score of MMH in the growth zone under the EMJ is about 300 (**Figure 4c**) (19). Note that the EMJ is irregular (**Figure 4b**), a process that begins in adolescent uteri, as basal endometrial stromal cells turn into muscle cells in the postpubertal burst of myometaplasia (40). Note also that the endometrium stains more darkly for ER (and PR) (**Figure 4b**) because endometrial stromal cells have scant cytoplasm, resulting in higher cellularity.

This growth zone was first described by Bird and Willis in 1965, who noted that in adult uteri, endometrial stromal cells appear to give rise to smooth muscle at the EMJ (49). This was confirmed by us in our study of MMH in adolescent and young adult uteri (14). Our recent study of myometrial growth and development demonstrated that this same process occurs in 2nd trimester fetal uteri (40). In fetal uteri, we refer to this as inframucosal myometaplasia, which is distinguished from intramural myometaplasia and subserosal myometaplasia (4). Most myometrial growth in utero is due to myometaplasia rather than mitotic proliferation. The pubertal burst of myometrial growth appears to be due to a burst of inframucosal myometaplasia, which can culminate in MMH in adolescent uteri (40). Paradoxically, the spindle cells seen by Bird and Willis at the EMJ do not always stain for actin, and may therefore be spindle shaped endometrial stromal cells, as seen by us in 2nd trimester fetal uteri (40).

We have suggested that inframucosal, intramural, and subserosal MMH in adult uteri are due to reactivation of myometaplasias that occurred in fetal uteri 10,40). This raises the possibility that if a medical treatment can be discovered to retard progression of reactivated inframucosal myometaplasia, it may some day be possible to prevent the need for hysterectomies due to both clinically significant MMH (17), and to fibroids – for which MMH appears to be a precursor (16).

In our experience the morphometric score for normal outer myometrium is around 1 (intensity) times 40 (% nuclei stained) =40 (**Figure 4d**)(19). It should not be surprising that this difference from MMH is statistically significant; given the obvious difference on microscopic examination (**Figure 4b,c,d**). Note, however, that

there is usually a gradual gradient (**Figure 4b**). Deeper MMH, in the middle third, is older than MMH right under the EMJ; since it is apparently displaced deeper in the wall as new MMH accrues over the years. Thus, senescent middle third MMH generally merges indistinguishably with normal outer myometrium on H&E (17) and on ER/PR stains.

Regression in MMH (**Figures 4e,f,g**) is different from senescence of middle third, older MMH (**Figure 4b**). It can manifest smaller nuclei than normal (10), focal cell shrinkage (**Figure 4e**), focal fibrosis (15), or patchy cell dropout (**Figure 4f,g**). Regression of MMH might conceivably lead to reduced myometrial contractility. If one believes the metropathy theory that non-neoplastic myometrial pathology may contribute to abnormal bleeding (7,17,20), such findings might be clinically relevant.

Myometrial dysfunction in MMH might also be due to desminopathy or actinopathy. We have documented desmin positive cytoplasmic globules in MMH (19)(**Figure 5a**), proving that desminopathy can occur in the myometrium. This should not be surprising, since desminopathy can affect skeletal muscle, cardiac muscle, and both gastrointestinal and vascular smooth muscle (50,51). We have also demonstrated decreased actin staining in MMH (19), raising the question of actinopathy, as can occur in the gastrointestinal tract, where it may cause pseudo-obstruction (52). However, staining artifact cannot be excluded until confirmatory molecular studies of actins in MMH are performed.

Myometrium is a complex, highly athletic muscular tissue

Not only did the crusade against unnecessary hysterectomies escalate at a point in time that was a nadir in collaborative clinicopathologic research on benign hysterectomies, it also antedated a modern understanding of the myometrium. Most important has been the realization that the uterus undergoes regular subclinical inner wall contractions during menstrual cycles (53-55). Even more striking is the discovery that the myometrium can contract in different directions (56). It can help expel menses by pushing downward; but it can also help propel sperm upward when intercourse follows ovulation, directing the sperm to the tubal ostium on the same side on which ovulation occurred. The nonpregnant uterus is not quiescent, but rather a complex, active, and athletic muscular organ. We suggest that this renders it susceptible to "athletic" injuries, analogous to those in skeletal muscle. These injuries can lead to naturally occurring scars with elastosis (**2a,5b,5c,5d**), and the resulting dysfunction can induce focal scar-associated myocyte hypertrophy to compensate for scar-induced myofiber disarray (**Figures 5b,e**) (21).

Elastosis of the uterus

There is beginning to be a better understanding of elastosis of the uterus, which we regard as a healing reaction in a moving tissue. Leppert and Yu showed that normal myometrial elastic fibers are so inconspicuous that they cannot be seen with the Elastic Van Gieson stain (57). Yet it has been known for 100 years that massive globular perivascular elastosis (in fibrosis uteri) can be seen in the middle and outer wall in naturally occurring myometrial scars (**Figure 2a**). (35,36). This can be evident on routine H&E stains, but is more conspicuous with special stains (**Figure 2a**) (58,59). We suggest that these may usually be healed reactions to tears

in the outer myometrium that occurred in the course of uterine contractions during pregnancy long before hysterectomy, accounting for the historical correlation of elastosis with parity (34-36). These abnormalities seem to occur at perivascular weak points in the wall, just as colonic diverticula occur at perivascular weak points in the wall of the colon (60).

Florid inner wall globular elastosis can be seen after ablations and endomyometrial resections (21). In our experience, massive globular elastosis can also be seen in unstable C-section scars (21), and it has been reported after myometrial injury by diathermy (36). In contrast, the more delicate abnormality of fibrillar elastosis (demonstrable with elastic van Gieson stains) has been identified in the outer wall in areas of pressure-induced edema and in proximity to serosal adhesions, constituting evidence of minor tissue damage (**Figure 6a**) (21).

We recently noticed that inner myometrial globular elastosis (**Figures 5b,c**), subtler than that observed in the outer wall (**Figure 2a**), can be commonly observed in hysterectomies performed for pain, in association with inner wall vascular ectasia (Figure 3d) as a sign of increased intramural pressure (18). We suspect that this was missed in previous studies of myometrial elastic tissue because they did not examine hysterectomies performed for pain (58,59). When inner wall elastosis extends into the basal endometrium (**Figure 5d)**, it also provides a possible mechanical explanation for abnormal bleeding. We suspect these are healing reactions to microscopic tears that occur during the subclinical contractions of menstrual cycles (53-56). Focal myocyte hypertrophy is part of this healing reaction (**Figure 5e**). We view such tears as intrauterine counterparts of athletic injuries that

commonly occur in skeletal muscle. Studies of uterine innervation suggest that these tears may be symptomatic because nerve endings for pain sensation are mainly in the inner third of the wall (61,62). Since pelvic pain may depend not only on tissue damage, but also on pain hypersensitivity (63), it is not surprising to us that we have sometimes seen inner myometrial elastosis in hysterectomies performed primarily for abnormal bleeding. We have also observed this lesion in cases of fibroid uterus and adenomyosis associated with pain; where it is located adjacent to the fibroids or adenomyosis

Similarly, florid neural proliferation after deep ablations (**Figure 6b)**, in patients with post-ablation pain symptoms, can be interpreted as postablation neuromas (64). Outer wall perineural elastosis (**Figure 6c)**, possibly reflecting a tear around a major nerve in the outer wall, also merits further study as a possible cause of pain leading to hysterectomy. It is well known that traumatic neuromas of soft tissue can be painful. Chronic neuritis of the myometrium (**Figure 6d**) also merits study as a possible cause of pain.

CONCLUSIONS

It is well known to gynecologists and their patients that women with pelvic pain attach a high value to identifying a cause for their pain; but this is often a humbling travail (65). Silverberg pointed out long ago that the majority of instances of abnormal uterine bleeding had no demonstrable organic cause in the endometrial curettage - a category referred to then as "dysfunctional uterine bleeding" (DUB)

(43). Although criteria were later developed for identifying cases of bleeding due to anovulation and other hormonal disorders (66), there still remain many cases in routine practice where the clinical diagnosis is DUB, and the pathologic diagnosis is ordinary proliferative or secretory endometrium (44). In both scenarios, failure to suggest possible pathologic explanations for the symptoms that led to hysterectomy can stress the doctor-patient relationship.

It is ironic that although Silverberg's monograph was published when modern knowledge about the myometrium had not yet been discovered; this monograph nonetheless took the view that when pain and/or bleeding leads to hysterectomy, this scenario challenged the fundamental responsibility of the surgical pathologist to demonstrate what and where is the lesion for which surgery was performed (9). It was said that the patient-surgeon-specimen-pathologist chain is the cornerstone of surgical pathology practice, since it is through the specimen that the pathologist makes contributions to the surgeon's knowledge and in turn the patient's well-being and peace of mind (67). It was written that the approach to this challenge determined how well surgical pathologists discharge their responsibility, not only to clinicians and patients, but also to themselves, their colleagues, and their profession (9). We think of these ideas as the Silverberg Principles, which appear to have been routinely ignored in pathology reports on benign hysterectomies as a lingering effect induced by the underperforming big and entrenched idea of unnecessary hysterectomy, which Silverberg so carefully considered (1,2). Figure 7 documents the likely pathogenesis of bleeding and/or pain in many clinically

abnormal uteri that have long been signed out as histologically normal, using standard textbook criteria. More research is needed in this area.

In summary, we believe that pathologists should attempt to provide possible explanations for otherwise unexplained pelvic pain and/or abnormal uterine bleeding. It is argued here that possible explanations should be offered - if there are objective findings, and if there is a rational scientific basis to support interpretations. In the final analysis, it must be up to the clinical judgment of the gynecologist to decide whether such tentative explanations are satisfactory answers, in the context of the complex details of each individual case. It is time to consider that the oft-repeated phrase "The pathologist could find nothing wrong with your uterus" is being said too often to too many patients by too many gynecologists. Close collaboration and communication between gynecologists and pathologists in the realm of hysterectomies for benign disease may foster future research to further evaluate the plausibility of these ideas.

RECOMMENDATIONS

In order to try to address the needs of patients and clinicians for a pathology-based explanation for the symptoms and signs leading to benign hysterectomy, we recommend the following approach:

1. Attempt clinicopathologic correlation with physical examination, and pelvic ultrasound findings, including “thickened endometrial stripes”. In some cases, this may include correlation with CT or MRI imaging findings.
2. When myomas are present, calculate the Myoma Index (number of myomas x size (cm) of largest myoma) to try to distinguish incidental myomas (Myoma Index <3.7) from clinically significant myomas (17). Myoma Index is a crude tool, but is evidence-based.
3. Interpret Myoma Index in the context of uterine weight, myometrial thickness, and postfixation gross photographs; which may be necessary to document grossly obvious pale firm inner MMH that may greatly exceed the volume of myoma tissue, and be most responsible for pressure effects. New slices after complete formalin fixation give the best gross photos. When adenomyosis is focal and microscopic, check gross photos for concurrent grossly obvious MMH that may better explain pressure effects. In some cases, all 3 disease processes may contribute significantly to increased intramural pressure.
4. Evaluate for pressure effects such as endometrial vascular ectasia, inner myometrial vascular ectasia, inward and outward bulges, and outer wall pressure effects (edema and vascular ectasia). Note intravascular and extravascular thrombi in relation to endometrial vascular ectasia. Note grossly obvious subserosal ridges that may deflect pressure inwards and

promote both inner myometrial vascular ectasia and inner myometrial elastosis.

5. Evaluate for inner myometrial elastosis in hysterectomies for pelvic pain or dysmenorrhea. This can be missed if trichrome or elastic stains are not done, and if less than 4 sections of uterine corpus (2 anterior, 2 posterior) are examined.

6. Take care to distinguish inner myometrial elastosis from postablation scars and outer wall scars (fibrosis uteri), which may have massive globular elastosis. Myofiber disarray and globular elastosis in C-section scars may be seen in some cases of bleeding from the lower uterine segment, whose clinical presentation simulates placenta creta previa (21).

7. If bleeding persists after ablation, check for vascular ectasia in scars that reach the endometrial surface; best seen on trichrome stains. Check for hemosiderin in the scars or in residual endometrium.

8. If pelvic pain increases after prior ablation for bleeding, do S100 stains to look for postablation neuromas (64). Utility of S100 stains in other hysterectomies for pain needs further study at this time (64); but increased inner wall nerves may be seen in cases where a clinical diagnosis of endometriosis lacks pathologic confirmation (64).

9. Pending further clinicopathologic research, report findings as possible explanations, subject to the clinical judgment of the gynecologist who knows the full clinical story.

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Legends for Illustrations

Figure 1a – Globoid outward bulging uterus as received in Pathology was obvious from a glance across the room. This tends to correlate with the history of a clinically enlarged uterus.

Figure 1b – After 48 hours of formalin fixation, cut surface of anterior wall (top) shows pale firm inner myometrial hyperplasia causing outward bulging of congested outer myometrium. Cut surface of posterior wall is very different, which is often the case.

Figure 1c – Inward bulge of myometrium is grossly obvious in freshly opened uterus. This can be detected on ultrasound. Note 2-3 mm pale firm subserosal ridge (arrow), which tends to deflect increased intramural pressure inward. Inframucosal MMH was not pale until after 48 hours of formalin fixation.

Figure 1d – Myocyte hypertrophy. Uterus weighed over 250 grams, after long term Depo Provera therapy. Huge smooth muscle cells have low N/C ratio. Side by side comparison to normal myometrium is provided by the adjacent Figure 1f.

Figure 1e – Chronic myometritis. Myofiber disarray is present, as seen after myometrial cell destruction by ablation. Hypertrophic smooth muscle cells are present in this area.

Figure 1f - Eosinophilic myometritis. Actin stain confirmed loss of muscle cells amongst the eosinophils.

Figure 2a – Fibrosis uteri in postmenopausal uterus. Outer myometrium has perivascular fibrosis on trichrome stain. Arteries have increased collagen

(arteriosclerosis). Pale unstained globules were positive on Elastic van Gieson stain (globular elastosis).

Figure 2b – Inner myometrial fibrosis was associated with long term use of Mirena IUD. This could be considered a type of fibrosis uteri.

Figure 2c – Markedly dilated subserosal lymphatics (top right), due to pressure effect caused by large subjacent fibroid.

Figure 2d – Markedly dilated vessels in outer myometrium reflect increased intramural pressure, caused in this case by MMH, as can be seen on gross exam (Figure 3c).

Figure 2e – Pressure effect of outer myometrial edema is well demonstrated on trichrome stain. Cause was inframucosal MMH (11,17).

Figure 3a – Marked endometrial vascular ectasia due to increased intramural pressure. These vessels can be seen on hysteroscopy (42). Red cell extravasation can manifest as ecchymoses that can also be seen on hysteroscopy (42).

Figure 3b – Myometrial hyperplasia (MMH) has increased cellularity and N/C ratio. This can vary from a subclinical structural variation to a clinically significant pathologic entity that is grossly detectable and associated with pressure effects (17,18).

Figure 3c – Clinically significant MMH in a well fixed uterus has firm pale myometrium occupying inner two thirds of wall. Color and texture resemble that of fibroids, but no nodule is present. Outer wall has conspicuous dilated vessels, due to pressure effects.

Figure 3d – Inner myometrial vascular ectasia may reflect increased intramural pressure, with deflection of pressure inward by subserosal ridge (Figure 1c). This pressure effect is anomalous. (Trichrome stain).

Figure 3e - CD31 immunostain (18) shows the usual slitlike inner wall vessels amidst inframucosal MMH.

Figure 3f - Outer wall vessels are rounded and dilated on CD31 stain (18), as seen grossly (Figure 3c) and on H&E (Figure 2d).

Figure 4a – Trichrome stain of postpartum hysterectomy shows residual gestational hypertrophy of myocytes (top left), and shrunken myocytes due to involution of gestational myocyte hypertrophy (bottom left). There are individual pyknotic myocytes (dark red, bottom center), due to involution of gestational myocyte hyperplasia. Intracytoplasmic hyaline globules (green) are characteristic of the process of apoptosis, although they can also stain red (48).

Figure 4b –Endometrium is strongly positive for ER (or PR), much darker than myometrium. Inframucosal MMH is poorly demarcated from normal outer myometrium on low power, giving the appearance of a gradient in intensity of staining, which gets progressively weaker with depth.

Figure 4c - Estrogen (or progesterone) receptor stain shows increased cellularity, nuclear size and N/C of actively growing MMH at growth zone under the endomyometrial junction.

Figure 4d -Normal outer myometrium has weaker staining for ER (or PR), in a smaller proportion of cells.

Figure 4e – Focal regression of inward bulging inframucosal MMH is visible on actin stain, although it was not obvious on H&E stain. (Inset) - High power photo shows zone of shrunken muscle cells.

Figure 4f – Tigroid pattern of muscle cell dropout in regressing MMH was obvious on actin stain.

Figure 4g - Cell dropout in MMH was subtler, but nonetheless obvious on routine H&E stain.

Figure 5a – Desmin positive cytoplasmic globules are proof of desminopathy in MMH (50).

Figure 5b – Interstitial globules of inner myometrial elastosis were detected on review of routine slides from hysterectomy done for pain. Location can also be perivascular. Color can vary from grey to pale pink to red, depending on quality of H&E stain..

Figure 5c– Elastic van Gieson stain of inner myometrial elastosis, shows perivascular pattern of distribution.

Figure 5d – Elastosis in basal endometrium is demonstrated by elastic van Gieson stain. Microscopic tears of the basal endometrium, leading to this healing reaction, may provide a mechanical explanation for abnormal bleeding.

Figure 5e –Focal hypertrophic myocytes (near inner myometrial elastosis) are part of the reaction to tissue damage in inner wall MMH.

Figure 6a – Fibrillar elastosis in outer myometrium is seen with Elastic van Gieson stain. This is evidence of tissue damage, since normal elastic fibers in the uterus are too small to be seen (57).

Figure 6b – Postablation neuroma has innumerable nerve twigs in inner myometrium on S100 stain, two orders of magnitude greater than normal uterine innervation.

Figure 6c – Perineural elastosis around large nerve of outer myometrium may reflect tissue damage that, like trauma to large nerves of soft tissue, may be a cause of pain.

Figure 6d – Chronic neuritis is considered a legitimate cause of pain by neuropathologists. Key criterion is endoneural location of lymphocytes. Chronic neuritis of the myometrium merits study as a possible cause of pelvic pain.

Figure 7 - A. The prototypical hysterectomy for abnormal bleeding from a clinically enlarged uterus has bulky myometrial hyperplasia (MMH) leading to an outward bulge, outer pressure effects (OPE), and endometrial vascular ectasia (EMVE) with extravasated red blood cells. Small myomas (M) may be present. B. The prototypical hysterectomy for pelvic pain due to bulky MMH may have inward deflection of increased intramural pressure by a subserosal ridge (SSR), leading to an inward bulge detectable on pelvic ultrasound, inner myometrial vascular ectasia (IMVE), and inner myometrial elastosis (IME). Findings may be patchy and heterogeneous, and many cases may have admixed or intermediate features of type A and type B.