**Essay.**

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# The pathophysiology of "constipation".

[1] **Wenzhou Medical University, Wenzhou, Zhejiang, PR 325000 China,**
[2] **Shenzhen University General Hospital, Shenzhen, PR 518055 China,**
[3] **Shanghai Jiao Tong University, Xujiahui, Shanghai, PR 230000 China.**

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**Correspondence:**

**Department of Obstetrics and Gynaecology,**
**International Peace Maternity and Child Health Hospital,**
**Shanghai Jiao Tong University,**
**910 Hengshan Road, Xujiahui, Shanghai, CHINA, PR 2300**

**Abstract**

"Constipation" may mean small, hard, or, straining over infrequent stools that are "difficult to pass", or in this context, persistent, physical efforts during defaecation (PPEDD). Significant proportions of Western populations (ca. 30%) undertake recurrent, valsalva manoeuvres during defaecation in the sitting position. Their sphincters are open, pelvic floors relaxed, and, they are vulnerable to injuries to their autonomic nervous system. Watching women in the second stages of their first labours also provides clear evidence of many, inefficient and ineffective patterns of straining that cause wide-ranging injuries. Autonomic nerves do not stretch, they tear, and, their injury has varied and unpredictable consequences that result in different patterns of "Western", non-communicable diseases (Table 1) in, and possibly beyond, the pelvis.

Three, distinguished gastroentrologists; Sir William Arbuthnot Lane, Bt., DP Burkitt, FRS, and KW Heaton, FRCP, made important anatomical and physiological observations that underpin this view of the origins of some, non-communicable, diseases. In obstetrics and gynaecology stage IV, nulliparous "endometriosis", vulval and vaginal pain, irritative bladder and bowel syndromes, pre-eclampsia, IUGR, placenta abruption, etc. may all result, in part, from varied, consequences of injuries to pelvic autonomic nerves. Injuries to branches of the cardiac, coeliac and pelvic plexi are not uncommon in the clinical literature in different non-communicable diseases, though the neurovascular pathways to, and from, the respective viscera have not been systematically examined in this context.

**Key words: Constipation, straining during defaecation, valsalva manoeuvre, hypertension, autonomic nerves, denervation, reinnervation.**

"Constipation" has different meanings for different people. Most understand it as "infrequent passage of stools"; others as "small, hard, or, difficult to pass, stools" – sometimes with a sensation of incomplete evacuation (1). In 1993, 1% of an urban, English population achieved defaecation once per week whilst 0.1% were only successful once per month. However 20-30% of that same population required physical efforts to start, or finish, evacuation using recurrent valsalva manoeuvres in the sitting position (2). In different people, at different times of life, varying patterns of straining during defaecation cause injuries to autonomic nerves at different levels of the sympathetic nervous system (T1-L2) with wide-ranging, pathophysiological consequences (3, Fig. 1; Table 1). Suggesting relationships between "constipation" and Western (non-communicable) diseases has always been "controversial"; nevertheless the original observations of three eminent clinicians deserve review in the context of new information about the causes and consequences of autonomic injuries (Figs.1-3).

**Sir William Arbuthnot Lane, Bt, CB, FRCS, (1856-1943),**

In 1924, WA Lane, the leading, London surgeon of the Edwardian era produced a remarkable account of the consequences of "chronic intestinal stasis" (4). He described "chronic intestinal stasis" in association with a number of different, clinical conditions and intra-abdominal physical signs. Lane found that many of his patients with ulcerative colitis, rheumatoid arthritis, Still's disease, gout, and many others, "improved" after abdominal adhesiolysis or colectomy.(4) In 1913, at a meeting of the Royal Society of Medicine a particularly sharp critique severed his relationships with many colleagues in London, and, in 1920 he left medical practice to establish the "New Health Society". This new organisation promoted whole foods, fruits and vegetables, sunshine and exercise with a plan to foster health and longevity through "three bowel movements per day".

**DP Burkitt, FRS, FRCS, (1911-1993), Trinity College, Dublin.**

DP Burkitt made two major contributions to medical science related to his experiences in Africa. The first was the description of the distribution, and ultimately, aetiology of Burkitt's lymphoma. The second was comparing different patterns of disease in Europe and Africa, to conclude that poor diets and lifestyles were the important antecedents of many Western, or, non-communicable diseases. In 1973, he showed that reduced stool weights (110 v 464g) and increased oro-anal transit times (40 v 12 hours) in Europeans compared to Africans, were associated with many Western disesases (5). "High fibre" diets were recommended, but sprinkling fibre on breakfast cereals was never a comprehensive solution to impaired Western diets and bowel habits. He was also, intrigued by the effectiveness of the squatting position for evacuation, though he was unable to articulate the precise reason for its preventing disease ? We now know that sitting on the toilet permits potentially harmful, physical efforts during defaecation whereas "squatting" prevents them.

**KW Heaton, FRCP, (1936-2013), University of Bristol**

Finally, Dr KW Heaton, FRCP, one of Burkitt's students, left us the Bristol Bowel Chart and the Bristol Bowel Survey. He found that 1% of an urban, Bristol population only achieved successful

defaecation once per week, and, only 0.1% achieved defaecation once per month (2, 6, 7). The latter group usually had a form of neurological injury to their bowel diagnosed as "slow transit constipation" - sometimes termed "Lane's disease". The final, and most important, observation of Dr. Heaton's East Bristol survey was that 20-30% of people "used physical efforts to start, or finish, defaecation" (2). Dr Heaton's epidemiological surveys on bowel habit permit precise, "permissive" questions such as "How often do you open your bowels – once per day, once per week, or once per month ?", and, "Do you have to strain to start or finish evacuation ?" Both questions produce significant, diagnostic returns in contemporary gynaecological clinics.

## Mechanisms of autonomic neurovascular injury

Squatting with your knees against your chest makes it difficult to perform recurrent valsalva manoeuvres, whereas in the sitting position it is possible to perform many different, straining efforts that may have consequences for autonomic nerves in the thorax, abdomen and pelvis at different times of life, in different shapes and sizes of human beings. The key pathophysiological mechanism is straining with your pelvic floor relaxed and your sphincters open; autonomic nerves do not stretch – they break - with profound and wide-ranging consequences (Table 1). Sitting on porcelain commodes became popular in the UK in the second half of the nineteenth century following TF Crapper's successful designs of porcelain, water closets and other sanitary products in Chelsea since 1861. (8) By the time WA Lane was performing colectomies in the Edwardian era (1900-1920), at least two generations had been exposed to these autonomic injuries. Defaecation after colectomy is an altogether different task; one indirect effect of his procedures may have been to remove the need for physical effects during defaecation.

The histologic hallmark of straining during defaecation is perivascular, nerve fiber proliferation where large numbers of injured nerves erupt from injured, nerve bundles releasing cytokines and nerve factors that act on adjacent, denervated arterioles to cause hyperplasia of their vessel walls (Fig. 2 Row 1a-c). The combined, neurovascular lesion (Fig. 1b) exhibits "new" and novel, P2X3 "stretch", VEGF, and, TRPV-1 "pain" receptors (Fig. 1c) that may be part of the mechanism for some of the ensuing consequences though, there is often a latent period of 5-10 years before the onset of clinical symptoms (7, 9, 10 Table 1). Lengthy, latent periods may have obscured the origins of many non-communicable diseases. They may be more apparent in women because of the effects of oestrogen-dependent hyperplasia and increases in pelvic blood flow in the second half of the menstrual cycle that lead to enlargements of the uterus (myoma, adenomyosis, etc.) and cyclic, pelvic pain (chronic pelvic pain, vulval pain, "endometriosis") respectively.

## Clinical consequences in the female pelvis

Prolonged and persistent, physical efforts during defecation are the antecedent of nulliparous vulval, vaginal, vesical and uterine pain that depend on the size and shape of the woman, and, the precise pattern of straining (3). No two individuals strain in exactly the same way, creating a variety of injuries at different anatomic sites, from infancy to old age. Watching women, in the second

stage of their first labors, attempting to deliver (or not deliver) their baby, is particularly instructive – but an insight that is only available to obstetricians ? Clinical apposition of the consequences of straining on the toilet, and, straining during childbirth have no analogies in other clinical specialties.

At present, the "causes" of autonomic neurovascular injury in the female pelvis are physical efforts during defecation, difficult first labors, hypertension, and, surgery and drugs for evacuation of the uterus; Some of these injuries leave detectable signs in the female pelvis that are readily detectable at laparoscopy (Fig. 3a-d). Potential visceral consequences include most of the chapter headings from a textbook of general pathology including tissue hyperplasia (leiomyoma, adenomyosis) , visceral dysfunction (endometriosis), ductal dysmotility (endometriosis), "opportunist" infection (vulvovaginal Candidiasis, preterm labour), arterial stenosis with ischemia (placental abruption), thrombosis (IUGR, small-for-gestational age infants), viscero-visceral reflexes(preeclampsia), aberrant reinnervation (endometriosis, interstitial cystitis, irritable bowel syndrome), and, chronic pelvic pain (Table 1).

The best example of injury through straining during defaecation is stage IV nulliparous "endometriosis" where adolescent, physical efforts result in fusion of rectum and vagina, hyperplasia of the uterosacral ligaments and injuries to their contained uterotubal nerves leading to retrograde menstruation, and, adhesion of ectopic endometrium to sites of tissue injury. (7) The male analogue to "endometriosis" is chronic "prostatitis" or the male "pelvic pain" syndrome that may extend to include interstitial cystitis-prostatitis-urethritis; as the female syndrome may also extend to include chronic pelvic pain-cystitis-urethral syndromes. Premenstrual symptoms of any description in a woman's pelvis should elicit questions about her bowel habits and duration of the second stage of her first labour, and, histopathological studies looking for injured perivascular nerves ? (3, 7)

## Clinical consequences beyond the female pelvis

Clinical medicine lists a large number of chronic, non-communicable, diseases with unexplained neural abnormalities and empirical treatments. Recurrent clinical presentations to many different clinical departments with disappointing clinical outcomes, are the clinical hallmarks of regional "neuropathic" pelvic pain syndromes. Retrocaecal appendicitis may be a clinical presentation of injured visceral autonomic nerves and recurrent straining and it, too, has had its share of neurological interest. (11, 12) Taking a careful history in women with inflammatory bowel diseases frequently discloses persistent physical efforts during defaecation though the anatomical site of the neural injury may vary between Crohns disease, ulcerative colitis and indeterminate colitis (13) ? Straining in supine, bottle-fed infants may lead to denervation of pancreatic islets and type 1 diabetes mellitus whereas similar efforts in another infant may lead to denervation-reinnervation of bronchioles – which have substantive stroma to enable regrowth of nerves - and early-onset asthma (14, 15) ? Making surgical incisions is sufficient to cause lifelong, chronic, neuropathic

pain syndromes in a worrying proportion of patients that may, in part, reflect the aetiology of the underlying condition (16).

Hyperplasia of the tunica media in umbilical arteries and uterine arterioles occurs in fetal, pregnancy and adult hypertension (9, 17-20). "Fetal hypertension" is defined as hyperplasia of the tunica media in the extra-fetal, umbilical artery resulting from, among other causes, injuries to the vasomotor nerves in the intrafetal umbilical artery with wide-ranging neurological consequences for the baby that may result in unexplained death (17, 18). Injuries to renal arterioles *in utero* may contribute to later neonatal, childhood, pregnancy and adult hypertension as a "direct" mechanism for DP Barker's "fetal origins of adult disease" hypothesis (18, 21). Less severe injuries to other viscera may embed neurovascular "discontinuity" in different organs that may also pave the way for later "neuropathic" disease (18) ?

We observe similar injuries to vasomotor nerves in both pregnancy and adult hypertension (19, 20), though there are no other plausible explanations of arteriolar stenosis since Moritz and Oldt described narrowing of visceral arterioles in hypertension in 1937 (9, Fig. 2). Hypertension is a lifelong diathesis associated with injuries to autonomic vasomotor nerves that extends from 18 weeks gestation to adulthood. Straining on the toilet may injure both uterine and renal nerve bundles that share segments of the sympathetic nervous system (T10-L2) in a proportion of hypertensive patients (22). Recurrent valsalva manoevres may be particularly dangerous during hypertensive pregnancy where "spikes" of blood pressure may lead to "fulminant" pre-eclampsia or eclampsia ?

## Conclusions

Autonomic injuries caused by persistent, straining efforts during constipation, or, prolonged childbirth are a feature of contemporary obstetrics and gynaecology, but, there is also evidence of "unexplained" autonomic injury in a wide range of extra-pelvic diseases ? Do the clinical and scientific observations of WA Lane, DP Burkitt and KW Heaton, provide for an understanding of the aetiology of some of these diseases when linked to the ubiquitous, neurovascular injuries associated with physical efforts during defaecation ? Even if these relaionships are established, they are clearly only one mechanism of autonomic injury and the recent descriptions of "fetal hypertension" syndromes offer another pathway to embedded, neurovascular injuries that may contribute to later adult disease. However, subtle distinctions between the effects of straining on the toilet, and straining in a first labour, or, the effects of oestrogen-dependent hyperplasia in the uterus and oestrogen-dependent blood flow in the second half of the menstrual cycles, are clearly not the daily experience of gastroenterologists. Taken together with our "losing" the full morphology of the autonomic nerves in vats of formalin in the post-1945 medical schools, it is not surprising that these distinguished gastroenterologists did not have all the necessary information to fully establish the relationships between our diets, bowel habits and subsequent diseases ?

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**Table 1**

1) **Tissue hyperplasia.** Endometrial hyperplasia (adenomyosis), and, myometrial hyperplasia (leiomyoma), are consequences of estrogen-dependent hyperplasia following denervatory injuries.
2) **Tissue hypoplasia.** In non-estrogen -dependent tissues there is often atrophy of denervated tissues e.g. bladder, bowel, vagina, vulva, etc.
3) **Loss of visceral function.** Early pregnancy loss, loss of cervical function in labor (cervix will not dilate), or at hysteroscopy (cervix will not open easily) are all examples of loss of visceral function in the female pelvis associated with injuries to pelvic autonomic nerves.
4) **Loss of visceral motility.** Dyspolar uterine and tubal motility leads to infertility, retrograde menstruation, and, dysfunctional labour.
5) **Opportunist infection** E.coli, vulvovaginal Candidiasis, bacterial vaginosis in gynecology are examples of "opportunist" infection following primary vulvovaginal denervation.
6) **Pain** Reinnervation leads to "pain in response to light touch" (hyperalgesia or allodyniae) e.g. dysmenorrhea, vulvovaginal pain, "mesh" pain, etc Increasng pelvic blood flow in the second half of the menstrual cycle frequently generates "light touch".
7) **CNS sensitization** Interstitial cystitis, chronic pain syndromes, postmenopausal pain, chronic vulval pain, etc are all examples of "central sensitisation" syndromes that has previously been associated with post-scar, pain syndromes e.g. following Caesarean section, hysterectomy, etc
8) **Induction of purinergic. "stretch" receptors** as secondary mechanisms of intercellular communication e.g. preeclampsia, the onset of primigravid labour, etc. Denervation of the uterus induces P2X3 "stretch" receptors that may play a role in important biological mechanisms.
9) **Viscero-visceral reflexes** the "uterorenal reflex" (cf cardiorenal, heptorenal, lieorenal) leads to activation of a corticomedullary vascular "shunt" in some views of preeclampsia. Wider activation of the autonomic nervous system may include headaches, migraines, nausea, vomiting, restlessness, fatigue, etc.
10) **Ischaemia-thrombosis** Injuries to visceral vasomotor nerves cause narrowing of arterioles through secondary hyperplasia of the denervated arteriole. Pregnancy complications associated with ischaemia and thrombosis, including placental abruption and placental infarction may be consequences of narrowing of visceral arterioles.

**<u>Table 1:</u> Some, wide-ranging, pathological consequences of autonomic injury in the pelvis that may also apply to the origins of non-communicable conditions around the body.**

**Figure 1. The pelvic autonomic nerves prosected and preserved in alcohol (not formalin) as described by Robert Lee, 1841 and Franz Frankenhauser, 1867**

These nerves converge on the vaginal vault where they are vulnerable to injury during prolonged and persistent physical efforts during defecation, difficult first labours, and, some forms of gynaecologic surgery e.g. evacuation of the uterus. Pelvic sympathetic nerves (T10-L2) pass through the superior hyogastric plexus (1), hypogastric nerve (2), inferior hypogastric plexus (3), to enter the uterovaginal plexus of Lee-Frankenhauser (4), in combination with pelvic parasympathetic nerves from sacral segments S2-4 (5).

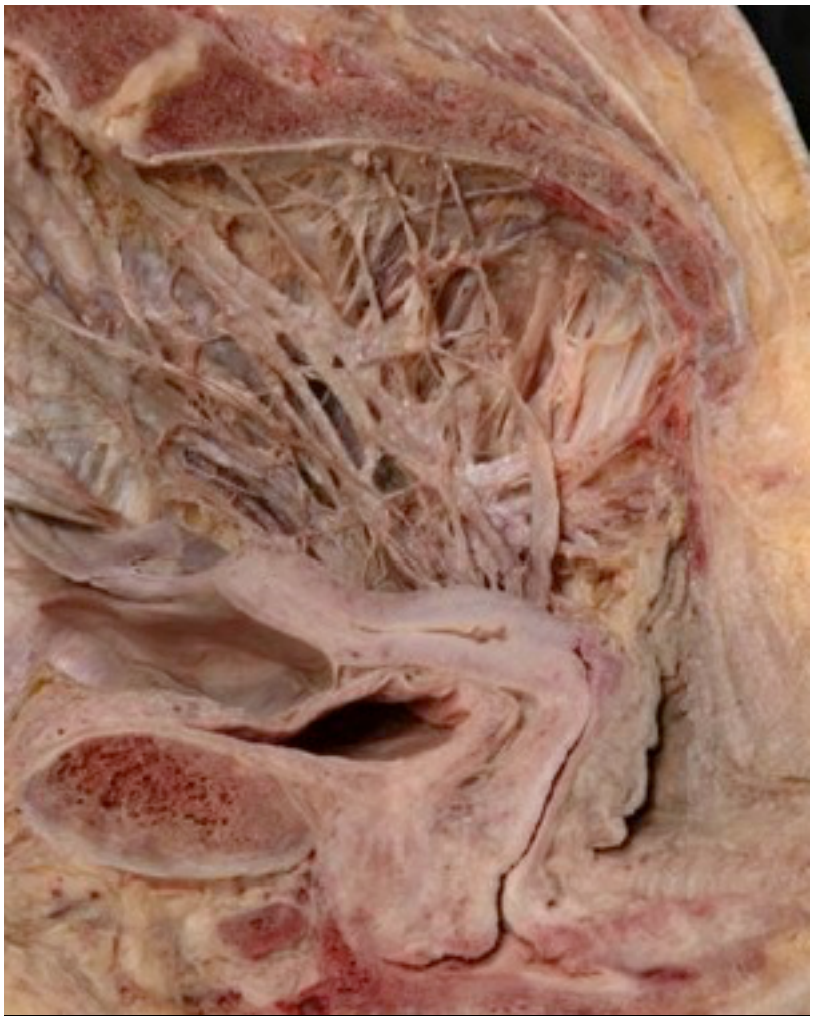
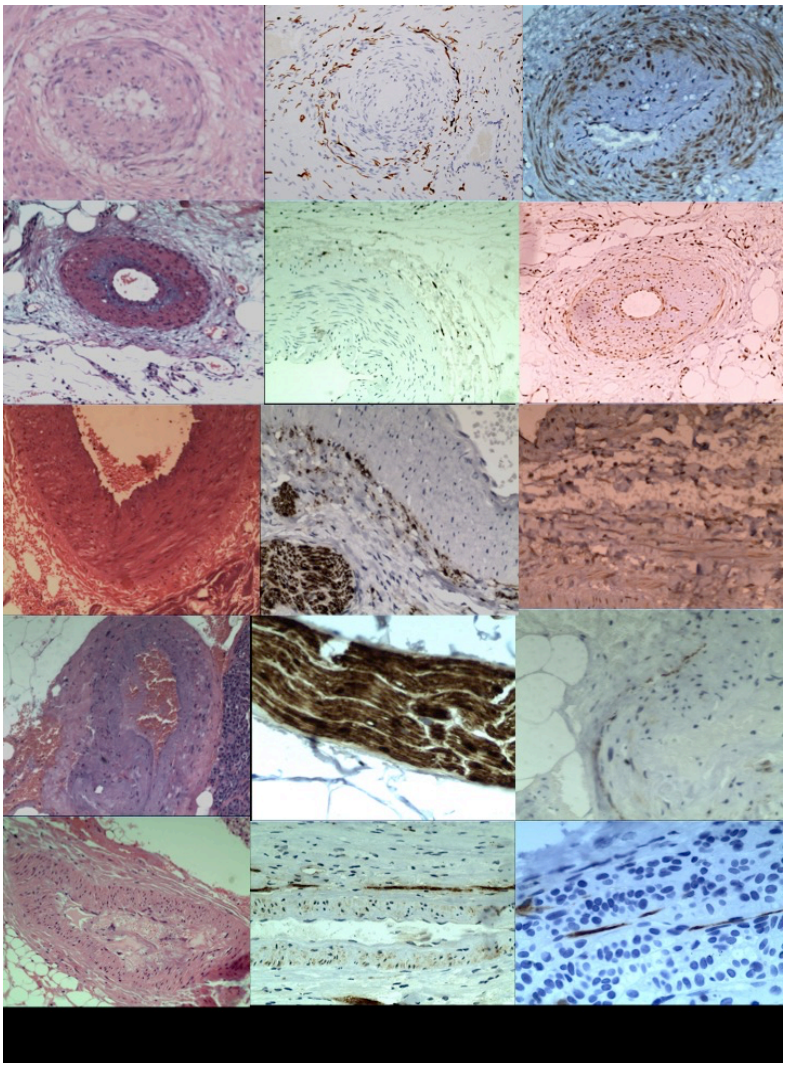


**Figure 2**

**Widespread injuries to visceral arterioles in adult hypertension discovered by Drs Moritz & Oldt, 1937 (Cleveland, OH) and, in the uterus by Dr AT Hertig, 1945, (Boston, MA). Row (1) is uterus, (2) kidney, (3) spleen, (4) pancreas, (5) adrenals. Column A is stained with hematoxylin and eosin, Column B is stained with anti-S100 antibody, Column C is stained with anti-P2X3 antibody. Only the uterus (1c) demonstrates positive staining for purinergic, "stretch" receptors that may be important to initiating pregnancy hypertension.**



Fig, 1 Row 1a shows narrowed uterine arteriole with a "halo of hyalinisation" in many of the "great" obstetric syndromes including preeclampsia, IUGR, placental abruption, preterm labour, midtrimester loss, unexplained stillbirth, etc (x100, HE)

Fig. 1 Row 1b shows narrowed uterine arteriole with a "halo of injured nerves" in the gynaecological syndromes including chronic pelvic pain with, or without, "endoemtriosis, vulval and vbaginal pain, irritative bladder and bowel syndromes, etc(x100, anti-S100)

Fig. 1. Row 1c shows narrowed uterine arteriole expressing P2X3, purinergic receptors in hyperplastic tunica media and intima that may be the initiating intrauterine mechanism in preeclampsia (x100, anti-P2X3)

Fig. 1.Row 2a-c shows narrowed arterioles from the hilum of the kidney demonstrating injured, *perivascular* renal nerves and early expression of P2X3, purinergic receptors in hypertension.

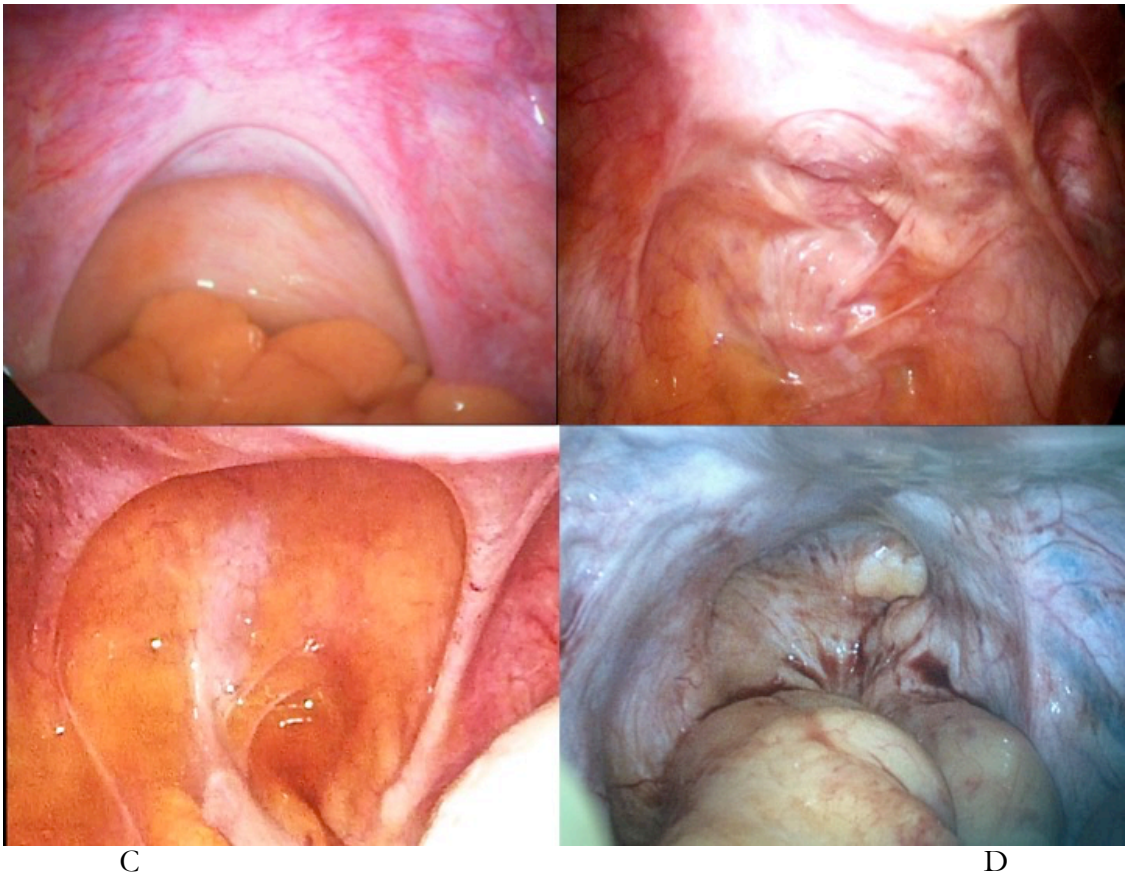
Fig.1.Row 3a-c shows narrowed arterioles from the hilum of the spleen demonstrating multiple layers of injured perivascular nerves (x100 Fig.1.iii.b)

Fig.1 Row 4a-c shows narrowed arterioles from the pancreas including a pancreatic nerve bundle with a U-shaped "cutting artefact" in its superior border as well as authentic *loss* of nerve fibers throughout the nerve bundle.

Fig.1 Row 5a-c shows narrowed arterioles from adrenals demonstrating adrenal cortical hyperplasia at x100 and x200 (5b-c) associated with injured pericortical nerves in this specific form of hypertension.

**Figure 3. Different patterns of injury to visceral neurovascular pathways – in this case the pelvic uterosacral ligaments that deliver autonomic nerves to the uterus and Fallopian tubes. They are visible at laparoscopy though their significance is often understated in the search for deposits of ectopic endometrium ("endometriosis")**

**A** **B**



C D

A = normal, nulliparous, uterosacral ligaments contain uterine and tubal nerves that supply the endometrial-myometrial nerve plexus and the proximal two thirds of the Fallopian tubes
B = asymmetric injuries to uterosacral ligaments with, on the left, complete avulsion of uterine and sacral origins, and, on the right, scarring of the uterine insertion and probable, avulsion of sacral origin. These are typical of asymmetric forces during vaginal delivery.
C = symmetric injuries to uterosacral ligaments with bilateral avulsions of sacral origins. These, unusual appearances are typical of excessive uterine activity in early pregnancy e.g. following administration of misoprostol for miscarriage or unwanted pregnancy. Attenuation of the ligaments, without clear avulsion typically occurs following excessive uterine activity following administration of prostaglandins or intravenous oxytocin.
D = complete absence of uterosacral ligaments. These appearances are unusual in Western gynaecology though is not uncommon in China during the "one-child" policy. These injuries usually follow one, or more, second trimester abortions; they result in infertility, ectopic pregnancy or diffuse, symmetric adenomyosis in later life.