

Article.

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**ORIGINS OF WESTERN DISEASE.**

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Western diseases are “those characteristic of modern, affluent, Western, technological communities (Table 1). In the second half of the twentieth century, three MRC Professors – DP Burkitt, PRJ Burch, DJP Barker - wrote books setting out their views of the aetiology of Western diseases based on original observations (1-3). Each set of studies carries reproducible, empirical observations requiring explanation by any subsequent hypothesis. This account reviews the “autonomic denervation” view of Western diseases in the context of these prior hypotheses (4).

### **DP Burkitt and the “dietary fibre” hypothesis**

In “Western Diseases: their emergence and prevention”, Dr DP Burkitt recorded that Africans eating low calorie, plant-based diets had short, intestinal, transit times (14 v 40 hours), increased stool weights (464g v 110g per day) with reduced rates of “constipation” compared to Europeans eating refined, high calorie diets (1). “Constipation” may mean small or hard stools, infrequent passage of stools, or, straining during defaecation; most clinical studies do not distinguish these different meanings (5). Affecting 2-27% of Western adults, it is more prevalent in women than men, children than adults, and, it is particularly common in preterm infants and postmenopausal women (6, 7). In an East Bristol population, Dr KW Heaton found that physical efforts during defaecation complicated 20-30% of Western bowel movements with 1% of adults opening their bowels less than once each week, and, 0.3% less than once each month (8). Recent studies confirm that persistent straining during defaecation causes neuropathic pelvic injuries in every organ in the nulliparous female pelvis, from the uterus to the vulva and the bladder to the rectum (9). Features of autonomic denervation and reinnervation also occur in many extrapelvic diseases on Burkitt’s list of Western diseases without clear aetiological explanations (4, Table 1).

### **PR Burch and the “stochastic” hypothesis**

Professor PRJ Burch published “Growth, Disease and Ageing” in 1968 (3). He posed the question; “why does the same disease have the same age of onset in well-defined and widely-separated populations?” For example, myasthenia gravis, duodenal ulcer and ulcerative colitis have similar, biphasic age distributions in New York, New Zealand and Norway. Each disease also has a similar “latent period” where the onset of visceral disturbance precedes the onset of clinical manifestations by some years. Before the present enthusiasm for genes and genomics, Burch adopted a genetic explanation for these observations though conceded there was “no logical necessity for the specific interpretation”. He argued that it was “simply not credible that sequential, deterministic biological clocks are distributed among individuals in many different populations so that they always “go off” according to a general stochastic equation.”

## **Professor DJP Barker and the “fetal origins” hypothesis**

Professor DJP Barker discussed observations in 31 of his papers in “Fetal and Infant Origins of Adult Disease” (3). Historical observations of birthweight and infant weight at one year in the first half of the twentieth century correlated with the later onset of cardiovascular and metabolic disease in the second half of the twentieth century. Typical observations showed that low birth weight infants with increased placental weights born in Preston between 1935 and 1943, had higher blood pressures at ages 46-54 than those adults with normal birth and placental weights. In a second series of observations of 370 Hertfordshire men, low birth weight and infant weight at one year were associated with an increased incidence of impaired glucose tolerance in later life. In both sets of observations, events in fetal and infant life provided biological markers for disease phenotypes presenting several decades later in the same individuals though without specific details of causal mechanisms.

## **The “autonomic denervation” hypothesis**

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Autonomic nerves supply our organs through sympathetic and parasympathetic divisions. Some organs receive autonomic nerves directly from the sympathetic chain and the vagus nerve while others pass through intervening plexi and ganglia with, or without, synapses. There is varying morphology and considerable complexity that may not have received sufficient attention in post-war medical schools since immersion in formalin destroys them (Figs. 1-2). The three, great, autonomic plexi - the cardiac (thorax), coeliac (abdomen) and hypogastric (pelvis) supply extrinsic innervation to their respective viscera (Fig. 2). Intrinsic visceral innervation varies from the complex interactions of Auerbach’s, Meissner’s and Henle’s plexi in small bowel to the subserosal and submucosal plexi in solid organs such as uterus and prostate (Fig. 3).

The autonomic denervation hypothesis proposes that injuries to autonomic nerves at different anatomical sites have diverse biological consequences resulting in varied, clinical presentations of Western diseases at different ages (4, Table 2). Causes of injuries to autonomic nerves include straining during defaecation, childbirth, trauma and surgery among others, whereas consequences are numerous, overlapping, diverse, and, operate at different ages (Table 2). Primary evidence derives from immunohistochemical studies of injuries to branches of the hypogastric plexus in different gynaecological conditions (10-12, Fig. 3a-d). Extrapolating these observations to branches of the cardiac and coeliac plexi offers explanations for unexplained denervation and reinnervation in other organs (4).

## The hypogastric plexus and gynaecological disease

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Large bundles of autonomic nerves converge on the junction of the uterus and vagina with the uterine arteries, and, in the uterosacral ligaments (Fig. 2). Both are susceptible to injury during childbirth. Two forms of injury to pelvic autonomic nerves result in two patterns of aberrant reinnervation; chaotic proliferative reinnervation and perivascular nerve fibre proliferation (Fig 3a-c). In the first pattern, intrapartum injuries to pelvic nerves result in re-growth of nerves from the proximal stump of the nerve bundle as it enters the uterine isthmus. Haphazard patterns of aberrant reinnervation result from a chaotic injury to the nerve bundle (12). Some years later light touch causes pain or discomfort (allodynia) (Fig 3b). Typical “allodynic” symptoms include some forms of chronic pelvic pain (10, 12), dysmenorrhea (12), vulvodynia (13), rectal hypersensitivity (14) and irritative bladder symptoms (15) i.e. benign gynaecology. In the second pattern, persistent, physical efforts during defaecation produces perivascular nerve fibre proliferation. Injured nerves re-grow along blood vessels encasing them in multiple, circumferential layers of abnormal nerves (Fig 3c). Premenstrual symptoms result from increases in blood flow during the second half of the menstrual cycle resulting in premenstrual uterine, vulval, vaginal and vesical pain (9). Similar histopathological patterns occur in myocardium (16), nasal turbinates (17) and intervertebral discs (18) and may reflect a longitudinal injury to the nerve bundle..

Consequences of autonomic injury at different sites in the lower genital tract result in different forms of gynaecological pathology. Focal injuries to nerves in the myometrium and endometrium, result in localized hyperplasia including some patterns of leiomyoma and adenomyosis (10, 11, Fig 3d). Injuries to nerves as they enter the organ result in chronic pelvic pain and endometriosis (12). Such injuries to peripheral autonomic nerves produce persistent, maladaptive plasticity in both peripheral and central nervous systems with recurrent, post-hysterectomy pain occurring in 10-50% of patients at five years (19). Similar patterns of chronic, disabling pain occurs following amputation (5-10%), mastectomy (5-10%), thoracotomy (10%), coronary bypass surgery (5-10%), inguinal hernia repair (5%), and, Caesarean section (5%) (19).

Denervation of epithelial surfaces also results in increased rates of opportunist and recurrent infections (20, 21). The combined denervatory effects of complicated childbirth and hysterectomy condemn many women to increasing rates of “constipation” in their later years (6).

## **The cardiac plexus and cardiovascular disease**

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Images of extrinsic cardiac innervation are rare and intrinsic myocardial innervation is complex (Fig. 2a). Aberrant myocardial reinnervation occurs with ventricular arrhythmias, cardiomyopathies and following myocardial infarction (16, 22, 23). Co-localization of Schwann cells, sympathetic nerves, and nerve axons suggests a relationship between ventricular reinnervation following myocardial injury and subsequent ventricular arrhythmias (16). Nerve sprouting may contribute to ventricular arrhythmia and sudden cardiac death, where myocardial infarction results in nerve injury that is followed by sympathetic nerve sprouting and aberrant myocardial reinnervation. Histological changes similar to those in uterine vessels with perivascular nerve fiber proliferation around coronary vessels, suggests the possibility that these lesions may contribute to some forms of angina while other pathological mechanisms contribute to myocardial infarction (24).

Hypertension and thrombosis are key determinants of chronic cardiovascular disease. Overactivity of renal sympathetic nerves in, and around, the wall of the renal artery are important in the initiation and maintenance of some forms of systemic hypertension (25, 26). Recent reports demonstrate sustained reductions in blood pressure after catheter-based renal denervation in patients with refractory hypertension (25, 26). There has been little work on the possible thrombogenic effects of denervation in the walls of varying diameters of blood vessel.

## **The coeliac plexus and abdominal disease**

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The coeliac plexus is part of the expanded plexus of autonomic nerves behind the stomach extending on to the crura of the diaphragm and along the anterior surface of the aorta. The three, splanchnic nerves connect with all the thoracic ganglia, and supply most of the organs in the abdominal cavity. Both have prolonged anatomical courses running in cranio-caudal planes to their visceral targets (Fig. 1a).

Type 1 diabetes mellitus (T1DM) has characteristic epidemiologic features of a Western disease with age-adjusted incidences varying from 0.1/100,000 per year in some Chinese provinces to more than 40/100,000 per year in Finland (27). Recent studies show evidence of pancreatic denervation of unknown aetiology in both rats and human (28, 29). Weaning before three months of age is associated with increased rates of constipation resulting in persistent physical efforts by the infant in the supine position that may lead to early, selective loss of sympathetic nerves in the islets of Langerhans (29). Other patterns of late-onset, organ-specific, “autoimmune” disease (OSAID) including thyroiditis, gastritis, pancreatitis,

adrenitis, coexist in women aged 50-80 and demonstrate similar histological features with infiltrates of CD4 and CD8 lymphocytes. Typically OSAID's coexist with similar diseases in adjacent organs in first degree relatives suggesting related aetiology. Autonomic denervation secondary to persistent, physical efforts during defecation or childbirth may cause primary visceral denervation rather than a primary "autoimmune attack" (30).

The mesenteric plexus receives nerves through the coeliac plexus as well as its own direct supply. Nerves are distributed from the oblique origin of the root of the mesentery to three intrinsic bowel plexi (Auerbach, Meissner and Henle) as far as the splenic flexure when ascending branches from the hypogastric plexi deliver similar patterns of innervation to the descending colon and rectum. Aberrant reinnervation occurs in some forms of oesophagitis, cholecystitis, chronic pancreatitis, inflammatory bowel disease, appendicitis, benign rectal disease, irritable bowel syndrome and anal fissures (4). Loss of autonomic nerves to the bowel occurs in Hirschsprungs disease, Crohns disease, ulcerative colitis colonic adenoma and some forms of diverticulosis in association with abnormal forms of visceral motility (4).

### **Related sources of morbidity**

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Persistent increases in intra-abdominal pressure contribute directly to herniae, hemorrhoids and varicose veins though may also contribute, indirectly, to disease at other sites (1). Their effects are compounded by contemporary rates of obesity. Aberrant reinnervation occurs in many other miscellaneous conditions as varied as allergic rhinitis, erosive lichen planus, Dupuytrens contracture, pulmonary hypertension, inttervertebral disc pain prostate cancer and pancreatic cancer (4). Many cancers may qualify as Western diseases and autonomic denervation may play a role in their pathogenesis though supportive evidence is limited (21).

## Conclusions

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Injuries to complex and varied pathways of autonomic nerves, contribute to different phenotypes of gynaecological disease. Causes of pelvic autonomic injury include straining during defaecation and difficult vaginal delivery. Different patterns of straining in different morphological shapes and sizes may contribute to autonomic injuries at different anatomical sites in the thorax and abdomen. Straining during defaecation is common at the extremes of age, particularly in preterm infants and postmenopausal women. Contemporary levels of obesity amplify the direct effects of increased intrathoracic and intra-abdominal pressures to contribute further swathes of morbidity. Autonomic denervation, and its consequences, explain some of Burkitt's seminal observations, offer answers to Burch's questions, and, connects Barker's low birthweight infants with subsequent disease phenotypes. Further studies of the causes and consequences of autonomic injury, may improve our understanding of the aetiology and pathogenesis of many chronic Western diseases.

## References

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- (1) Burkitt DP, Trowell HC.  
Western diseases: their emergence and prevention.  
Edward Arnold, 1981.
- (2) Burch PRJ.  
Growth, Disease and Ageing.  
Oliver and Boyd, Edinburgh, 1968.
- (3) Barker DJP.  
Fetal and Infant Origins of Adult Diseases.  
BMJ Group, 1992.
- (4) Quinn MJ.  
Autonomic denervation and the origins of Western disease.  
Med Hypoth 2010; 74:937-44.
- (5) Probert CS, Emmett PM, Cripps HA, Heaton KW.  
Evidence for the ambiguity of the term constipation: the role of irritable bowel syndrome.  
Gut 1994; 35(10):1455-8.
- (6) Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M.  
Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults.  
Arch Int Med 2001; 161:1989-1996.
- (7) Cunningham C, Taylor GH, Minich NM, Hack M.  
Constipation in very low birth weight infants at 10-14 years of age.  
J Ped Gastroenterol Nut 2001;33(1):23-7.
- (8) Heaton KW, Cripps HA.  
Straining at stool and laxative taking in an English population.  
Dig Dis Sci 1993; 38:1004-8.
- (9) Quinn M.  
Perivascular nerve fibre proliferation: the consequence of prolonged straining.  
J Obstet Gynaecol 2007; 27(2):185-8.
- (10) Quinn M.  
Uterine innervation in adenomyosis.  
J Obstet Gynaecol 2007;27(3):287-91.
- (11) Quinn M.  
Uterine innervation in fibroids.  
J Obstet Gynecol 2007; 27(5):489-92.
- (12) Atwal GSS, Duplessis D, Armstrong GR, Slade RJ, Quinn MJ.  
Uterine innervation after hysterectomy for chronic pelvic pain with, or without, endometriosis.  
Am J Obstet Gynecol 2005; 193:1658-1663.

- (13) Westrom LV, Willen R.  
Vestibular nerve fiber proliferation in vulvar vestibulitis syndrome.  
Obstet Gynecol 1998; 91:572-6.
- (14) Chan CLH, Facer P, Davis JB, Smith GD, Egerton J, Bountra C, Williams NS, Anand P.  
Sensory fibre expressing capsaicin receptor TRPV-1 in patients with rectal hypersensitivity and faecal urgency. Lancet 2003; 361: 385-91.
- (15) Schofield EC, Clausen JA, Burcher E, Moore KH.  
GAP- Immunoreactivity of subepithelial and detrusor muscle nerve fibres in patients with refractory idiopathic detrusor overactivity. Neurourol Urodynam 2005; 24:325-33.
- (16) Chen LS, Zhou S, Fishbein MC, Chen PS.  
New perspectives on the role of autonomic nervous system in the genesis of arrhythmias.  
J Cardiovasc Electrophysiol. 2007 Jan;18(1):123-7.
- (17) Figueroa JM, Mansilla E, Suburo AM.  
Innervation of nasal turbinate blood vessels in rhinitic and non-rhinitic children.  
Am J Resp Crit Care Med 1998; 157:1959-66.
- (18) Freemont AJ, Peacock TE, Goupille P, Hoyland JA, O'Brien J, Jayson MI.  
Nerve ingrowth into diseased intervertebral disc in chronic back pain.  
Lancet. 1997; 350(9072):178-81.
- (19) Kehlet H, Jensen TS, Woolf CJ.  
Persistent postsurgical pain: risk factors and prevention.  
Lancet. 2006; 367(9522):1618-25.
- (20) Straub RH.  
Autoimmune disease and innervation.  
Brain Behav Immun. 2007; 21(5):528-34.
- (21) Gemmill JA, Stratton P, Cleary SD, Ballweg ML, Sinai N.  
Cancers, infections, and endocrine diseases in women with endometriosis.  
Fertil Steril. 2010 Oct;94(5):1627-31.
- (22) Tan AY, Chen PS, Chen LS, Fishbein MC.  
Autonomic nerves in pulmonary veins.  
Heart Rhythm. 2007; 4(3 Suppl):S57-60.
- (23) Kimura K, Ieda M, Kanazawa H, Yagi T, Tsunoda M, Ninomiya S, Kurosawa H, Yoshimi K, Mochizuki H, Yamazaki K, Ogawa S, Fukuda K.  
Cardiac sympathetic rejuvenation: a link between nerve function and cardiac hypertrophy  
Circ Res 2007; 100: 1755-64.
- (24) Quinn MJ.  
Mechanisms of angina.  
Heart. 2009; 95(13):1108-9;

- (25) Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M.  
Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet*. 2009; 11;373(9671):1275-81.
- (26) Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD.  
Renal sympathetic-nerve ablation for uncontrolled hypertension.  
*N Engl J Med*. 2009, 27;361(9):932-4.
- (27) Feltbower RG, McKinney PA, Greaves MF, Parslow RC, Bodansky HJ.  
International parallels in leukaemia and diabetes epidemiology.  
*Arch Dis Child*. 2004;89(1):54-57
- (28) Mei Q, Mundinger TO, Lernmark A, Taborsky GJ.  
Early, selective, and marked loss of sympathetic nerves from the islets of BioBreeder diabetic rats.  
*Diabetes* 2002; 51(10):2997-3002.
- (29) Mei Q, Foulis AK, Fligner C, Hull RH, Gilliam L, Taborsky GJ.  
Selective loss of sympathetic nerves from the islet in human type I diabetes: a potential mechanism for impaired glucagon responses to hypoglycaemia.  
*Diabetes* 2006; 55:A15.
- (30) Quinn M  
“Autoimmune” conditions and autonomic denervation.  
*Am J Med* 2008; 121(8):e13.

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**Diseases of the bowel**

Appendicitis, diverticular disease, ulcerative colitis, polyps, cancer of the large bowel,  
*Oesophagitis, cirrhosis, chronic pancreatitis, Crohns disease, rectal hypersensitivity, anal fissures.*

**Diseases of cholesterol metabolism**

Coronary disease, gallstones, obesity.

**Raised intra-abdominal pressure**

Hiatus hernia, haemorrhoids, herniae, varicose veins

**Cardiovascular disorders**

Deep venous thrombosis, pulmonary embolism  
*Cardiac arrhythmias, heart failure, cardiomyopathy, post-transplant syndromes*

**Autoimmune diseases**

Type 1 diabetes, thyrotoxicosis, pernicious anaemia, rheumatoid arthritis, multiple sclerosis.  
*Sjogren's syndrome, hypothyroidism,*

**Miscellaneous disorders**

*Allergic rhinosinusitis, erosive lichen planus, asthma, Dupuytren's contracture, intervertebral disc pain.*  
*Gynaecological conditions including endometriosis, adenomyosis and fibroids.*  
*Pancreatic and prostatic cancer.*  
*Chronic postoperative pain following different surgical procedures.*

**Table 1**

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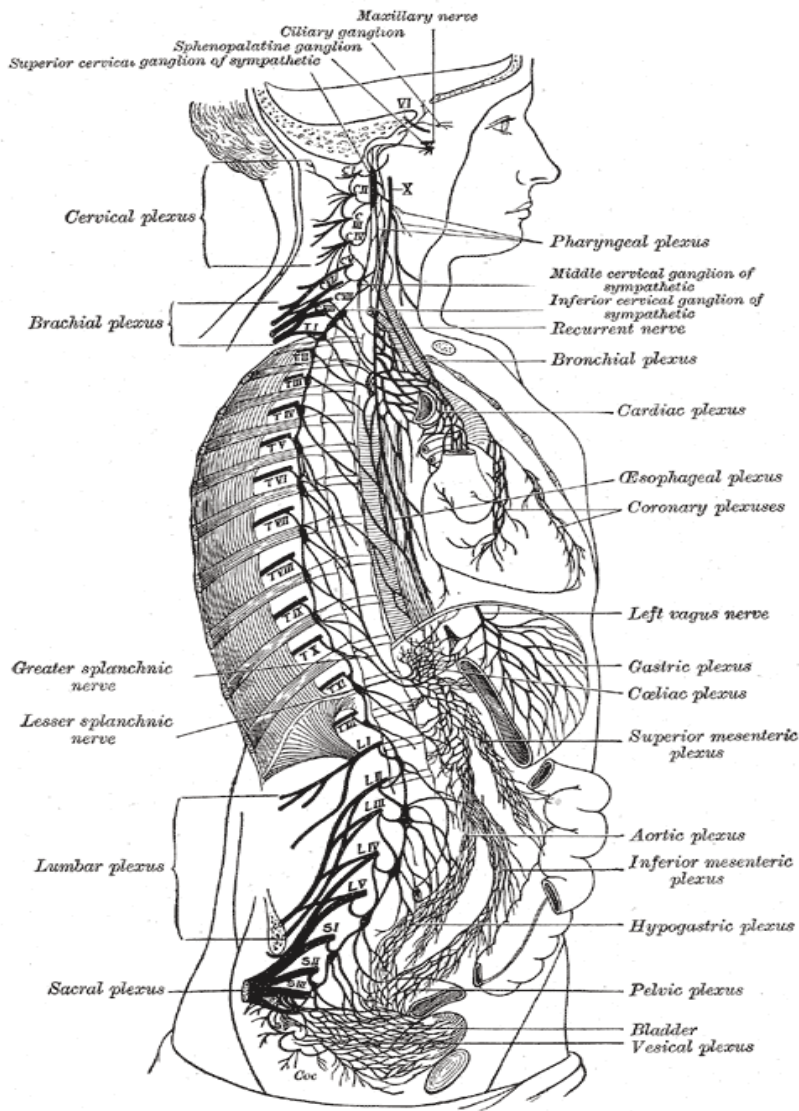
DP Burkitt's original diseases of Western civilization, BMJ 1973;1:274-278 along with diseases with more recent evidence of autonomic denervation and reinnervation (*in italics*).

Changes in form	(a) hypoplasia (b) hyperplasia	e.g. impaired bladder or bowel emptying e.g. adenomyosis, leiomyoma
Changes in function	visceral dysmotility	e.g. abnormal uterotubal dysmotility in endometriosis
Susceptibility to infection	(a) pathogenic infection (b) opportunist infection	e.g. recurrent vulvovaginal Candidiasis e.g. bacterial vaginosis in preterm labour
Aberrant reinnervation	(a) chaotic reinnervation (b) perivascular nerve fibre proliferation	e.g. multiparous endometriosis e.g. nulliparous endometriosis
CNS changes	CNS “memory” associated with aberrant peripheral reinnervation e.g. persistent pelvic pain after removal of all pelvic organs and endometriosis	

**Table 2**

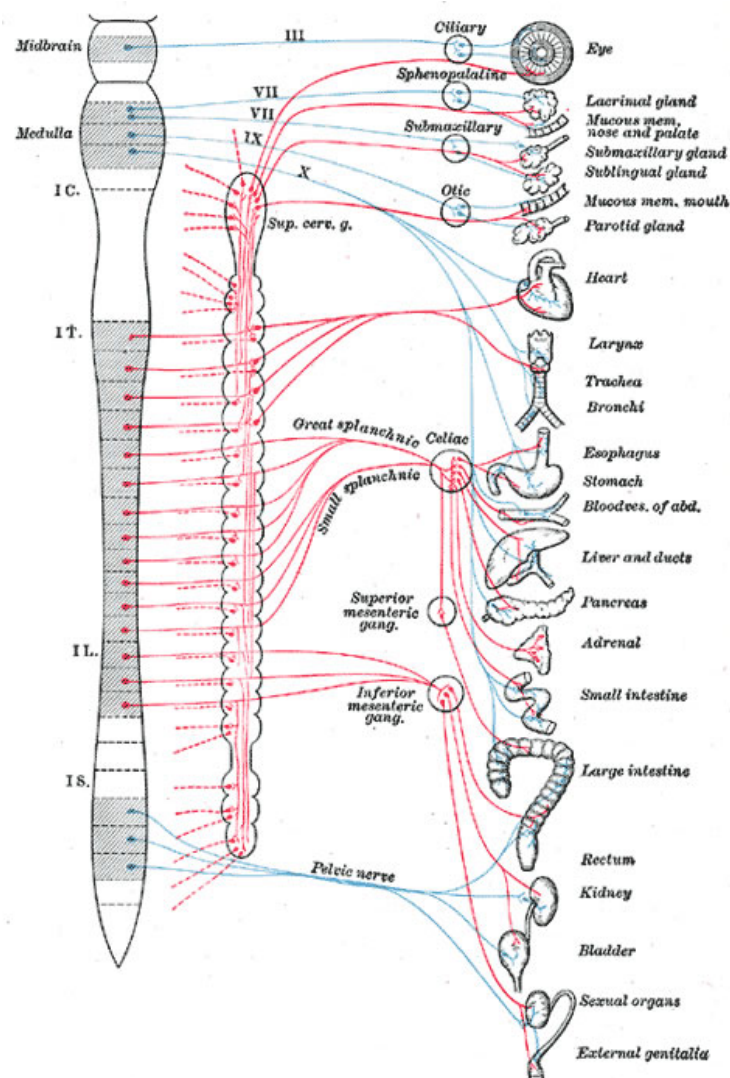
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Diverse consequences of autonomic denervation in the lower genital tract. Analogous consequences may occur at extra-pelvic sites in association with injuries to branches of other autonomic plexi including the cardiac and coeliac plexi.



**Fig 1a**

The right sympathetic chain and its connections with the thoracic, abdominal, and pelvic plexuses. (after Schwalbe, from Gray's Anatomy at [www.bartleby.com](http://www.bartleby.com) Fig 838. ). Note the concentrations of nerves in the cardiac (thorax), celiac (abdomen) and hypogastric (pelvic) plexi, and, the apparent “suspension” of different viscera by branches of the sympathetic chain.



**Figure 1b**

Neuroanatomical “wiring” of the autonomic nervous system. Parasympathetic nerves have a craniosacral outflow (III, VII, IX, X) whilst sympathetic nerves have thoracolumbar origins. Sympathetic nerves may, or may not, synapse in the sympathetic chain; intermediary neurons may diminish, or amplify, the effects of sympathetic stimulation, parasympathetic nerves tend to synapse in, or adjacent to, the viscus. Some autonomic nerves have short anatomical courses e.g. pancreatic nerves, whilst those supplying the small bowel traverse the mesentery, and, those supplying pelvic viscera traverse pre-aortic plexi and the pelvic side wall.

**Figure 2**

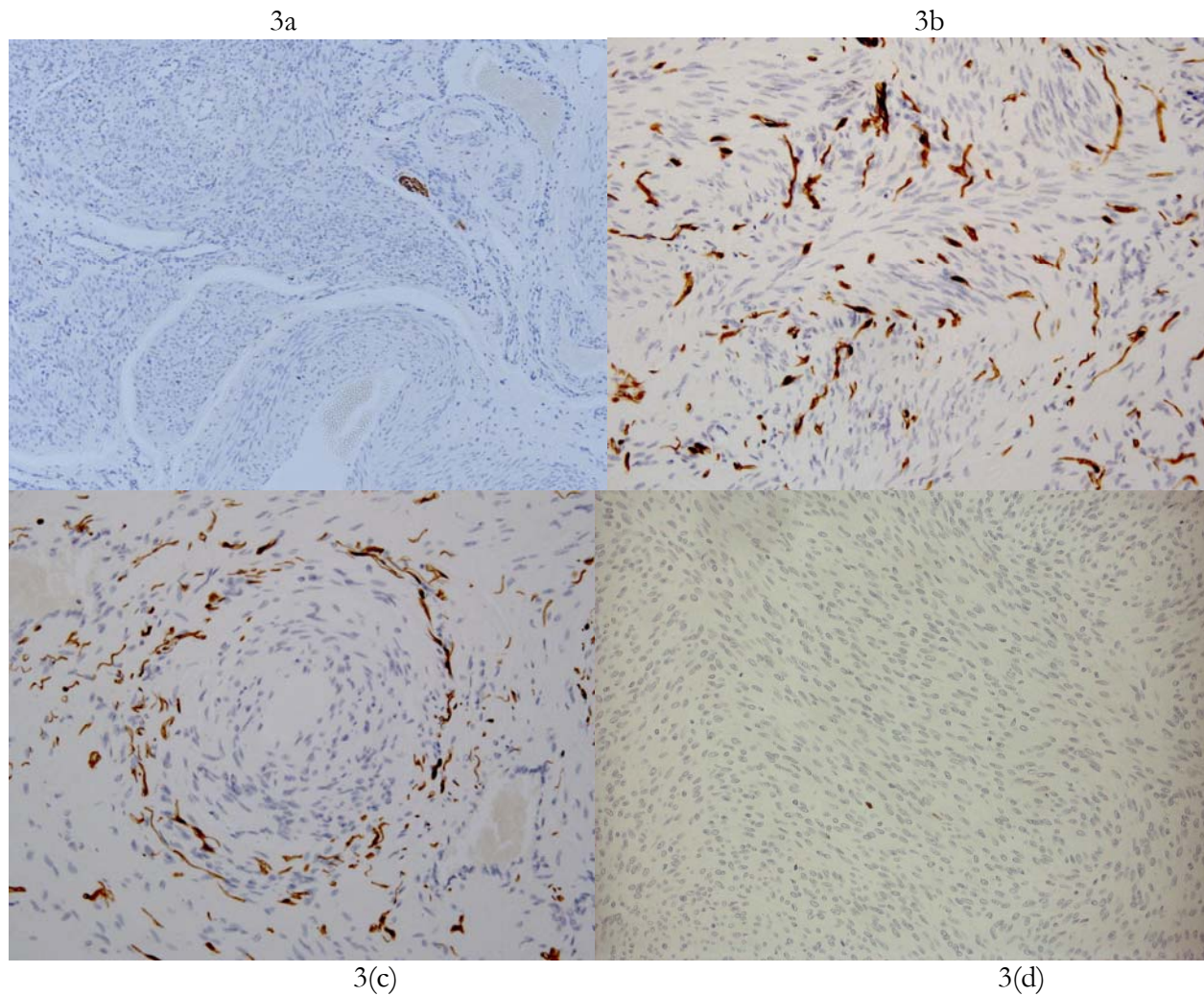
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**Figure 2**

The pelvic plexi dissected in methanol demonstrating the superior hypogastric plexus (A), (B) the hypogastric nerve, (C) the inferior hypogastric plexus, (D) the uterovaginal plexus of Frankenhauser and (e) pelvic parasympathetic nerves from S2-4. (University Department of Anatomy, Bristol, Spackman, 2007).

**Figure 3**



Clinical denervation and reinnervation in the female pelvis produces the three benign pathologies of endometriosis, adenomyosis and leiomyomas, as well as many clinical presentations including some forms of vulvodynia, dyspareunia, dysmenorrhea, chronic pelvic pain, irritative bladder and irritable bowel syndrome.

- (a) Normal myometrium is sparsely innervated (x100).
- (b) Aberrant reinnervation in the myometrium in chronic pelvic pain with "endometriosis" (x200).
- (c) Aberrant reinnervation. Perivascular nerve fibre proliferation after prolonged constipation (x200).
- (d) Denervation in the myometrium in leiomyoma (x200).