

Hypothesis.

Autonomic denervation and the origins of chronic Western disease.

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Abstract

Many Western diseases result from lifestyles that include refined, high calorie diets, poor bowel habits, limited physical exercise and suboptimal childbirth. Western diets give rise to reduced stool weights, increased bowel transit times and prolonged physical efforts during defaecation. Injuries to autonomic nerves result from prolonged physical efforts during defaecation or childbirth. Their consequences include changes in visceral form resulting from tissue hypoplasia or hyperplasia, changes in visceral function including dysmotility, increased susceptibility to infection, and, aberrant reinnervation with sensitisation of the central nervous system. Such injuries may also be vulnerable to other sources of autonomic dysfunction including stress, alcohol, smoking, drugs, and infection that may contribute to the onset and course of the disease. Specific injuries at different anatomical sites in autonomic pathways give rise to a wide range of Western diseases from infancy to old age, through diverse and cumulative mechanisms.

Key words: Western disease, diet, bowel habit, childbirth, autonomic denervation, reinnervation.

DP Burkitt contrasted different rates of disease in Western societies eating refined, high-calorie diets, and non-Western societies eating unrefined, low-calorie, plant-based diets (Table 1). He observed reduced stool weights (110g v 454 g per day), and, prolonged bowel transit times (40 v 14 hours) though he was unable to establish the underlying mechanisms of disease (1). This hypothesis proposes that prolonged physical efforts during defaecation and childbirth are primary, though not exclusive, sources of injuries to autonomic nerves resulting in a wide range of chronic diseases. Other sources of autonomic dysfunction including stress, alcohol, smoking, drugs and infection, may contribute to the onset, and, relapsing courses of many of these diseases.

Three autonomic plexi supply the chest, abdomen and pelvis respectively. The cardiac plexus lies between the pulmonary veins on the posterior surface of the left atrium, the coeliac plexus is behind the pancreas and the hypogastric plexi occupy the pelvic side walls (Fig.1). Nineteenth century anatomists, particularly Robert Lee at St Georges Hospital, made detailed drawings of the great autonomic plexi from fresh material preserved in alcohol (2). Few colleagues are familiar with their detailed anatomy since storage of cadaveric material in formalin destroys their finer detail, and, few surgical procedures take place around the autonomic plexi (3). Injuries to autonomic nerves (denervation) and their subsequent regeneration (reinnervation) take place throughout the body though the sources of injury are not clearly defined.

Straining during defaecation complicates 20-30% of Western bowel habits (4). As many as 1% of Western adults achieve successful defaecation less than once per week and 0.3% less than once per month (4). Prolonged, physical efforts during defaecation, and childbirth, cause injuries to autonomic nerves across the pelvis leading to subsequent gynaecological problems (5). Consequences of autonomic denervation in the female

pelvis include tissue hypoplasia and hyperplasia, visceral dysmotility, susceptibility to infection, aberrant reinnervation and sensitisation of the central nervous system (Table 2). Many clinical problems result from hyperalgesiae (“exaggerated response to a normal stimulus”), and, allodyniae (“light touch causes pain or discomfort”) secondary to aberrant reinnervation (6). These include chronic pelvic pain, dyspareunia, vulvodynia, frequency and urgency passing urine, irritable bowel symptoms, rectal hypersensitivity, dysmenorrhea, as well as the three benign gynaecological pathologies of endometriosis, adenomyosis and fibroids (7, 8). The disease “phenotype” depends, to some extent, on the site of the neural injury. Injuries to nerves entering the uterus result in chronic pelvic pain and endometriosis whereas injuries to the nerve plexus at the endometrial-myometrial nerve plexus leads to adenomyosis, and, injuries to myometrial nerves result in some forms of fibroids (7-9).

Autonomic neuroanatomy is complex and its details not essential to this account. The sympathetic nervous system has thoracolumbar origins with synapses in the ganglia of the paravertebral sympathetic chain and projects to other spinal levels, up and down the sympathetic chain. The parasympathetic nervous system has craniosacral origins, thoraco-abdominal distribution through the vagus nerve, and, ganglia adjacent to, or within, the viscus. Injuries to pre-ganglionic and postganglionic nerves have different effects. Unexplained autonomic denervation takes place in many other organs including endocrine glands subject to “autoimmune” disease e.g. parotid, thyroid, adrenals (10). Patterns of unexplained reinnervation also occur in other organs related to Burkitt’s list of chronic Western diseases including myocardium, oesophagus, liver, gall bladder, pancreas, appendix, kidneys, rectum and anus (11).

Injuries to short nerves to endocrine organs, for example to the pancreas, may have different causes and consequences from injuries to nerves running over long anatomical courses such as the nerve supply to the appendix (12, 13). If an injury disrupts or shears a nerve bundle completely then subsequent regenerative processes result in chaotic aberrant reinnervation (Fig 2b). Different clinical consequences arise from disruption of the nerve bundle along its longitudinal axis in its neurovascular bundle where perivascular nerve fibre proliferation (PVNFP) takes place (Fig. 2c). Abnormal nerves regenerate in concentric circles around the blood vessel resulting in premenstrual symptoms in different pelvic organs with increases in pelvic blood flow during the second half of the menstrual cycle (5). Increasing demands for blood flow in myocardium, where PVNFP also occurs, may result in angina pectoris, or, atrial and ventricular arrhythmias (14, 15). There are few studies of denervation of small or large-diameter blood vessels in relation to atherogenesis and thrombosis though there is current interest in the contribution of aberrant reinnervation in the renal arteries to refractory hypertension (16).

The effects of prolonged physical efforts during defaecation vary across different shapes and sizes, and, throughout our lifespans. The anatomical site of injury in a supine infant is likely to be different from that to an adult sitting on bathroom porcelain. Bottle-fed infants are more susceptible to bowel disturbances than breastfed infants (17) offering a plausible mechanism for loss of nerves to the pancreas in type 1 diabetes mellitus (12), and, an explanation for some of the beneficial effects of breastfeeding. In this view injuries to uterine nerves caused by persistent straining during defaecation in nulliparous women result in uterotubal dysmotility (7). Ensuing retrograde menstruation delivers ectopic endometrium to injured pelvic surfaces. Clinical symptoms result from aberrant reinnervation rather than ectopic endometrium that is largely a laparoscopic

epiphenomenon (7, 9). The remote consequences of childbirth and hysterectomy cause high rates of sustained defaecatory problems in elderly women that may, in turn, account for high rates of “autoimmune” disease (10, 18). Injuries to autonomic nerves may contribute to typical infiltrations by CD4 and CD8 lymphocytes that initiate the similar histopathological sequences in different organs in many “autoimmune” diseases. Stochastic relationships between incidence and age of onset show similar distributions for many “autoimmune” diseases, and indeed for many of DP Burkitts’ list of chronic Western diseases (19)

Unrecognized injuries to the autonomic nervous system may contribute, in part, to diminished host resistance. Antibiotic-resistant organisms and new opportunist infections infect tertiary health care in many Western countries. Multi-resistant *Staphylococcus aureus*, *Clostridium difficile* and *Clostridium welchii* are among the most prominent sources of antibiotic-resistant organisms in recent years. *Helicobacter pylori* has been identified as a variable source of morbidity in different upper GI conditions (20) while bacterial vaginosis, *Ureaplasma urealyticum* and group B streptococcus are common opportunistic organisms in the developing pandemic of preterm labour (21). The precise biology of contributory host factors, are not fully understood though may have wide-ranging impacts on the wellness of Western populations.

Persistent increases in intra-abdominal pressure contribute directly to herniae, hemorrhoids and varicose veins though may also contribute, indirectly, to disease at other sites (22). Obesity amplifies the effects in these conditions. Several neurological conditions, notably Parkinson’s disease and multiple sclerosis, have high rates of constipation that precede the onset of disease by many years (23, 24). Direct injuries to the brain and spinal cord may contribute to some aspects of pathogenesis in some

groups of patients. Aberrant reinnervation occurs in many other conditions as varied as intervertebral disc pain, allergic rhinitis, Dupuytren's contracture, pulmonary hypertension, prostate cancer and pancreatic cancer.

Testing this hypothesis will require evaluation in disease-specific contexts, and, further appraisal of sources of autonomic injury. Prevention of injuries to autonomic nerves requires radical changes to Western diets, improved bowel habits, better patterns of exercise, and, management of childbirth that is sensitive to unrecognised medium and long term, maternal morbidity (25).

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Figure 1

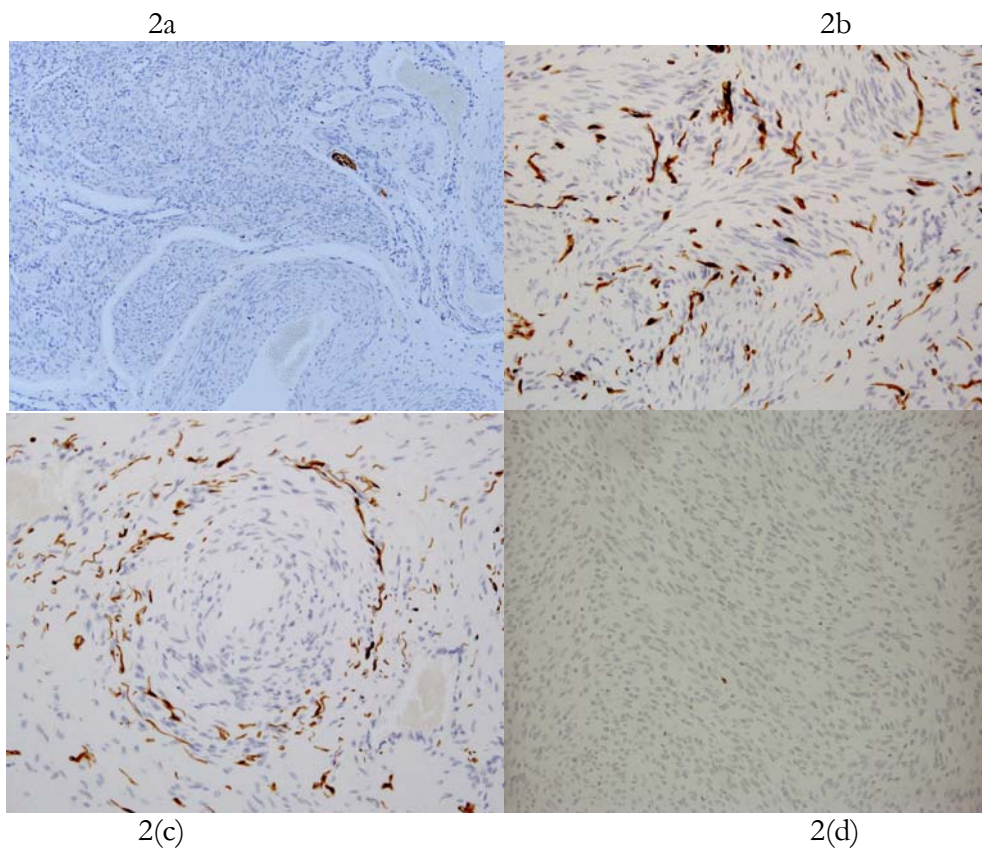


Figure 1

The hypogastric plexus dissected in cadaveric material embalmed in methanol in the University Department of Anatomy, Bristol (Spackman, 2007).

- A = superior hypogastric plexus
- B = hypogastric nerve
- C = inferior hypogastric nerve plexus
- D = uterovaginal (Frankenhauser's) nerve plexus
- E = sacral nerve roots at S2-4 contribute parasympathetic nerve fibres

Figure 2



- 2(a) Normal myometrium is sparsely innervated (x100).
- 2(b) Aberrant reinnervation in the myometrium in "endometriosis" (x200).
- 2(c) Perivascular nerve fibre proliferation in the myometrium (x200)
- 2(d) Denervation in the myometrium in leiomyoma (x200).