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Autonomic denervation and the origins of Western diseases

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SUMMARY

Many chronic Western diseases result from lifestyles that include refined diets, poor bowel habits, limited physical exercise and suboptimal patterns of childbirth. Prolonged physical efforts in the second stage of labour result in injuries to pelvic autonomic nerves leading to diverse and varied, gynaecological pathology including endometriosis, adenomyosis and fibroids. Western diets give rise to reduced stool weights, increased bowel transit times and persistent physical efforts during defaecation. Prolonged physical efforts during defaecation and childbirth may also cause latent, or direct, injuries to branches of the cardiac (thorax), coeliac (abdomen) and hypogastric (pelvis) plexi. Injuries to autonomic nerves result in impaired visceral function including visceral dysmotility, tissue hypoplasia and hyperplasia, increased susceptibility to infection, and, aberrant reinnervation with sensitisation of the central nervous system (CNS). These previously unknown injuries are vulnerable to the long list of causes of autonomic dysfunction, e.g. stress, alcohol, drugs, infection, trauma, cancer, etc. Specific injuries at different anatomical locations in midline autonomic pathways give rise to a wide range of Western diseases from infancy to old age, through diverse and cumulative mechanisms.

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Introduction

Burkitt recorded different distributions of chronic disease in Western and non-Western societies in association with marked differences in diet and stool weight [1,2], (Table 1). He was unable to define the underlying relationships between refined, high-calorie Western diets and diverse Western disease. Typical Western diets result in increased, bowel times (80 h vs. 34 h), reduced stool weights (110 g vs. 454 g each day) and constipation [1]. "Constipation" means small or hard stools, infrequent passage of stools, or, persistent, physical efforts during defaecation [3], though most clinical studies do not distinguish these different interpretations. Overall, it affects 2–27% of Western adults and is more prevalent in women than men, children than adults, and, in the elderly [4]. Physical efforts during defaecation complicate 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 [5]. Rates of constipation between the sexes are roughly equal until adolescence when there is a progressive and sustained increase in female constipation through the reproductive years into old age [4].

Sympathetic nerves, arising from thoracolumbar segments of the spinal cord, pass through paravertebral, sympathetic chains to visceral plexi while parasympathetic nerves have craniosacral origins from four cranial nerves (III, VII, IX, X) and three sacral

segments of the spinal cord (S2–4). 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 (Fig. 1). The three great autonomic plexi are the cardiac (thorax), coeliac (abdomen) and hypogastric (pelvis) that supply extrinsic innervation to their respective viscera. Intrinsic visceral innervation varies from the complex interactions of Auerbach's, Meissner's and Henle's plexi in small bowel to the sub-serosal and submucosal plexi in solid organs such as uterus and prostate. Immersion in formalin destroys fine, autonomic nerves so that many, twentieth century physicians have been unfamiliar with the fine, anatomical detail of the major autonomic plexi described by Robert Lee and other, nineteenth century anatomists [6,7] (Fig. 2a–c).

Autonomic dysfunction results from a long list of possible causes including alcohol, drugs, trauma, infection, cancer, that has not previously included the complications of persistent physical efforts in childbirth or defaecation [8], (Table 2). Many of these traditional causes will exacerbate the effects of specific injuries to autonomic nerves. New, immunohistochemical reagents provide reliable markers for denervation or subsequent, aberrant reinnervation that have been recorded in many, unrelated and unexplained, subspecialist contexts in recent years. Description of the range of gynaecological disease resulting from injuries to branches of the hypogastric plexi in the female pelvis offers a template for the consequences of denervation and reinnervation in cardiac, coeliac, and secondary autonomic plexi.

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Table 1
D.P. Burkitt's diseases of Western civilization, BMJ 1973;1:274-278.

Diseases of the bowel
Appendicitis, diverticular disease, ulcerative colitis, polyps, cancer of the large bowel
Diseases of cholesterol metabolism
Coronary disease, gallstones, obesity
Raised intra-abdominal pressure
Hiatus hernia, haemorrhoids, herniae, varicose veins
Venous disorders
Deep venous thrombosis, pulmonary embolism
Autoimmune diseases
Type 1 diabetes, thyrotoxicosis, pernicious anaemia, rheumatoid arthritis, multiple sclerosis

The inferior hypogastric plexus and gynaecological disease

Pre-aortic, nerve plexi divide into bilateral superior hypogastric plexi that converge on large, multilayered, nerve plates on the pelvic side wall (inferior hypogastric plexi) before distributing

nerves to the pelvic viscera (Fig. 3d). Large bundles of autonomic nerves converge on the junction of the uterus and vagina where they are susceptible to injury, particularly 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-d). In the first pattern, intrapartum injuries to pelvic nerves as they enter the uterine isthmus, result in re-growth of nerves from the proximal stump, and, chaotic patterns of aberrant reinnervation [9-12]. Some years later light touch causes pain or discomfort (allodynia) (Fig. 3b). Typical "allodynic" symptoms include some forms of vulvodynia [14], dyspareunia [15], chronic pelvic pain [16,17], dysmenorrhoeal [18], rectal hypersensitivity [19] and irritable bladder symptoms [20,21] i.e. benign gynaecology. In the second pattern, persistent, physical efforts during defaecation produces perivascular nerve fibre proliferation (Fig. 3d). Injured nerves regrow along blood vessels encasing them in multiple, circumferential layers of abnormal nerves. Symptoms relate to increases in blood flow during the second half of the menstrual cycle resulting in

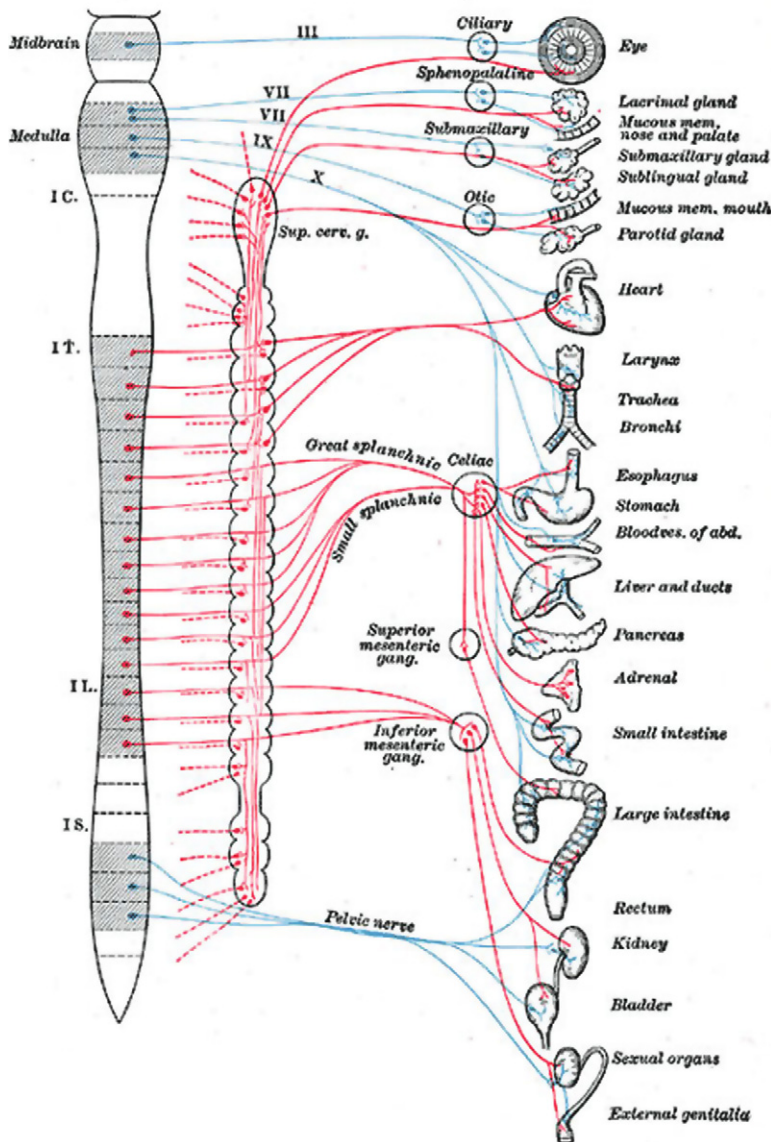


Fig. 1. Neuroanatomical "wiring" of the autonomic nervous system. Parasympathetic nerves have a craniosacral outflow (III, VII, IX, X) whilst sympathetic nerves have thoracolumbar origins. Sympathetic nerves may, or may not, synapse in the sympathetic chain; intermediary neurons may diminish, or amplify, 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.

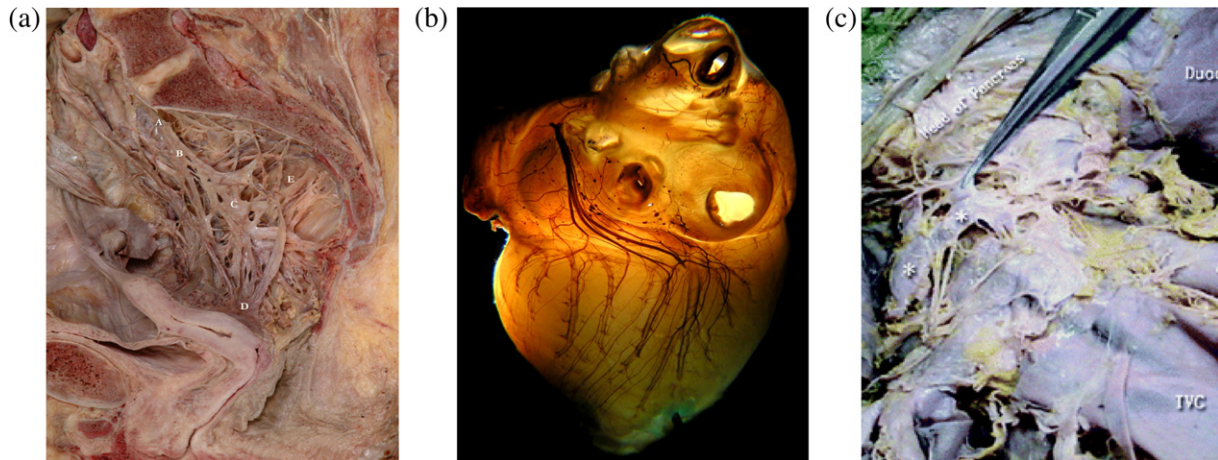


Fig. 2. (a) The hypogastric plexus dissected in methanol in the University Department of Anatomy, Bristol (Spackman, 2007). (b) The cardiac nerves demonstrated in a canine specimen (with permission, Professor DH Pauza, University Department of Anatomy, Kaunas, Lithuania). (c) The coeliac plexus dissected in alcohol (with permission, Professor XM Chang, Dept Radiology, North Sichuan Medical College, Sichuan, China).

Table 2
Traditional causes of autonomic failure (From Bannister R., *Autonomic Failure* Second Edition, OUP, 1988.). Persistent physical efforts during defaecation and childbirth can be appended to this list.

Primary
(a) Pure autonomic failure (formerly, idiopathic orthostatic hypotension)
(b) Autonomic failure with multiple system atrophy
(c) Autonomic failure with Parkinson's disease
Secondary
(a) Medical disorders, e.g. diabetes mellitus, amyloidosis
(b) Autoimmune disease
(c) Carcinoma
(d) Metabolic diseases, e.g. porphyria, Fabry's disease, Tangier disease
(e) Hereditary sensory neuropathy
(f) Infections, e.g. syphilis, Chagas disease, HIV, herpes zoster
(g) CNS lesions, e.g. tumours involving the hypothalamus
(h) Spinal cord lesions
(i) Familial dysautonomia and bradykinesia
(j) Aging
(k) Toxins, e.g. alcohol
(l) Drugs, e.g. anti-depressants, antihypertensives, tranquilisers

premenstrual uterine, vulval, vaginal and vesical pain [11]. Similar patterns occur in myocardium [22], nasal turbinates [23] and intervertebral discs [24].

Injuries 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 [25–29], (Fig. 3e–f). Vulvovaginal denervation results in local patterns of aberrant reinnervation, and, may underpin some pelvic infections including recurrent vulvovaginal Candidiasis, and, possibly, opportunistic vaginal organisms associated with the developing pandemic of preterm labour [30,31]. Injury to peripheral nerves produces persistent, maladaptive plasticity in both peripheral and central nervous systems [13]. Recurrent, post-hysterectomy pain occurs in 10–50% of patients at 5 years [32,33]. 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%) [34]. Different injuries at different anatomic sites may influence reproductive outcomes in subsequent pregnancies, and, contribute to later gynaecological problems. The combined denervatory effects of complicated childbirth and hysterectomy condemn many women to increasing rates of “constipation” in their later years.

Persistent physical efforts may cause further autonomic injuries resulting in some organ-specific, autoimmune diseases that are 10–20 times more common in women than men in older age groups [35–37] (Table 3).

The cardiac plexus and cardiovascular disease

Superior, middle and inferior cardiac nerves derived from T1–4 converge on the aortic arch to deliver sympathetic fibres to the cardiac plexus (Fig. 2b). Parasympathetic fibres derive from the vagus nerve. Branches appear from beneath the aortic arch to spread into the myocardium. Cardiac surgeons rarely disturb the posterior surface of the left atrium between the pulmonary veins that is the site of this plexus. Images of the extrinsic cardiac innervation are rare; intrinsic myocardial innervation is complex. Some remarkable dissections by Dr. Kawashima have provided some much needed clarity [38–39].

Ant myocardial reinnervation occurs with ventricular arrhythmias, cardiomyopathies and following myocardial infarction [40–42]. A relationship between ventricular reinnervation following myocardial injury and subsequent ventricular arrhythmias was demonstrated by co-localization of Schwann cells, sympathetic nerves, and nerve axons [40]. 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 [40]. Cardiac transplantation results in a time-dependent decrease in cardiac nerves followed by nerve sprouting in the anterior wall of the left ventricle, and, around intra-myocardial blood vessels [43]. Histological changes similar to those in uterine vessels with perivascular nerve fibre 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 [44].

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 systemic hypertension [45]. Recent reports demonstrate sustained reductions in blood pressure after catheter-based renal denervation in patients with refractory hypertension [45,46]. The evidence does not yet confirm that aberrant reinnervation occurs in, and around the renal arteries though it does follow renal transplantation and may contribute to some patterns of post-transplant hypertension [47]. There has been little work on the possible

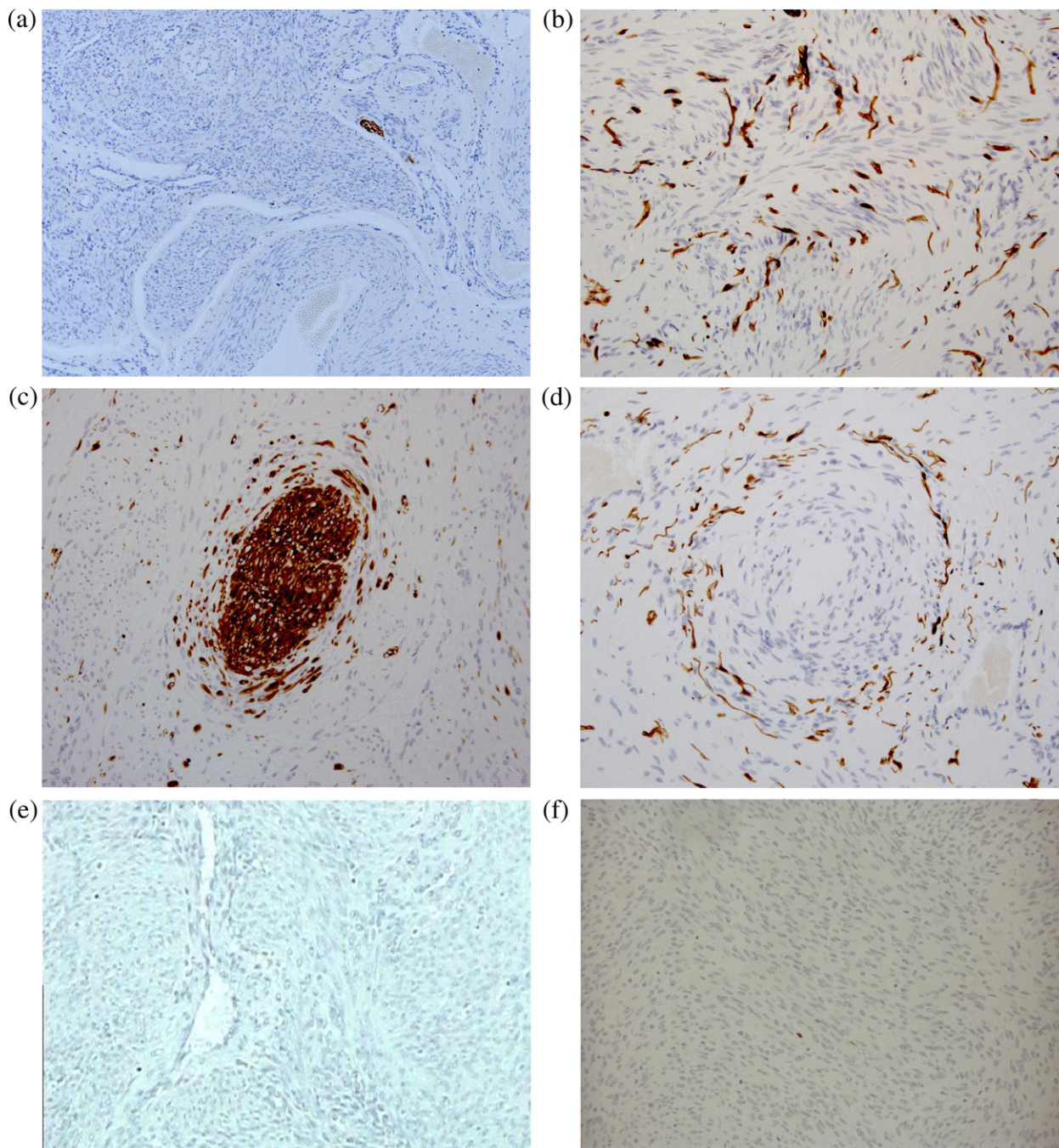


Fig. 3. (a) Normal myometrium is sparsely innervated (100×). (b) Aberrant reinnervation in the myometrium in “endometriosis” (200×). (c) Aberrant reinnervation. Collateral sprouting from a nerve bundle following vaginal delivery (200×). (d) Aberrant reinnervation. Perivascular nerve fibre proliferation after prolonged constipation (200×). (e) Denervation at the endometrial–myometrial interface in adenomyosis (200×). (f) Denervation in the myometrium in leiomyoma (200×).

167 thrombogenic effects of denervation in the walls of varying diam-
168 eters of blood vessel.

169 The coeliac plexus and abdominal disease

170 The coeliac plexus is part of the expanded plexus of autonomic
171 nerves behind the stomach extending onto the crura of the dia-
172 phragm and along the anterior surface of the aorta (Fig. 2c). It is
173 situated at the first lumbar vertebra (L1) and consists of two, large
174 celiac ganglia and a dense network of interconnecting fibres that
175 surround the coeliac and superior mesenteric arteries. This plexus
176 receives sympathetic nerves from the greater (T5–10) and lesser

(T9–10) splanchnic nerves as well as parasympathetic fibres from
177 the vagus. Secondary plexi include the phrenic, hepatic, lienal, re-
178 nal, gastric, aortic, superior and inferior mesenteric plexi. There are
179 striking similarities between the splanchnic and the cardiac nerves.
180 There are three cardiac nerves; they arise from all three cervical
181 ganglia, and supply the heart and lungs. The three, splanchnic
182 nerves connect with all the thoracic ganglia, and supply most of
183 the organs in the abdominal cavity. Both have prolonged anatom-
184 ical courses running downwards to their visceral targets.
185

186 Type 1 diabetes mellitus (T1DM) has characteristic epidemiol-
187 ogic features of a Western disease with age-adjusted incidences
188 varying from 0.1/100,000 per year in some Chinese provinces to

Table 3

Consequences of autonomic denervation in the lower genital tract. Similar consequences may occur at extra-pelvic sites in association with injuries to autonomic nerves

Changes in form	(a) Hypoplasia (b) Hyperplasia	E.g. impaired bladder or bowel emptying E.g. adenomyosis, leiomyoma
Changes in function	(a) Primary failure (b) Visceral dysmotility (c) Production failure	E.g. failure of decidualisation and pregnancy loss E.g. abnormal uterotubal dysmotility in endometriosis E.g. ovarian dysfunction in PCOS
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

more than 40/100,000 per year in Finland [48]. Recent studies show evidence of pancreatic denervation of unknown aetiology in both rats and humans [49,50]. Weaning before three months of age is associated with increased rates of constipation [51]. Persistent physical efforts by the infant in the supine position may lead to early, selective loss of sympathetic nerves in the islets of Langerhans. Other patterns of late-onset, organ-specific, "autoimmune" disease (OSAD) including thyroiditis, gastritis, pancreatitis, adrenalitis, coexist in women aged 50-80 and demonstrate similar histological features with infiltrates of CD4 and CD8 lymphocytes. Typically OSAD's coexist with similar diseases in adjacent organs suggesting related, anatomical aetiology. Autonomic denervation secondary to persistent, physical efforts during defecation or childbirth may account for their primary visceral denervation [35,36].

T1DM is one of three of the major childhood diseases that show marked epidemiological differences between Western and non-Western countries. Epidemiological studies show that T1DM, acute lymphoblastic leukaemia and asthma are prevented to some degree by exclusive breastfeeding for 6 months and have similar epidemiological distributions [52-54]. In this view, injuries to autonomic plexi supplying the pancreas, spleen and lungs may account for the loss of islet cells in the pancreas, white cell hyperplasia in the spleen, and, allergic rhinitis and bronchial hyperplasia in the lungs [51].

The mesenteric plexus receives nerves through the celiac plexus as well as its own direct supply. Nerves start from the oblique origin of the root of the mesentery to innervate three intrinsic bowel plexi (Auerbach, Meissner and Henle). At the splenic flexure 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 [55], chronic liver disease [56], cholecystitis [57,58], chronic pancreatitis [59], inflammatory bowel disease [60-63], appendicitis [64,65], benign rectal disease [66], irritable bowel syndrome [67,68] and anal fissures [69]. In one study of 816 appendices, 140 (17%) demonstrated features of aberrant innervation in three different histopathological patterns while 25% of normal appendices removed incidentally during other surgical procedures, showed features of aberrant innervation [65]. Loss of autonomic nerves to the bowel occurs in Hirschsprungs disease, Crohns disease, ulcerative colitis and some forms of diverticulosis in association with abnormal forms of visceral motility [70-77].

Related sources of morbidity

Persistent increases in intra-abdominal pressure contribute directly to herniae, haemorrhoids, hiatus herniae and varicose veins though may also contribute, indirectly, to disease at other sites [78]. Several neurological conditions, notably Parkinson's disease and multiple sclerosis, have high rates of moderate to severe constipation that precede the onset of each condition by many years [79-81]. Direct injuries to the brain and spinal cord may contribute

to some aspects of disease pathogenesis. Reinnervation in the CNS was a focus of early research in Alzheimers disease [82] and temporal lobe epilepsy [83] though has given way to genetic inquiry. Aberrant reinnervation occurs in many other miscellaneous conditions as varied as intervertebral disc pain [23], allergic rhinitis [24], Dupuytrens contracture [84], pulmonary hypertension [85], prostate cancer [86] and pancreatic cancer [87].

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 clinical problems in recent years. *Helicobacter pylori* has been identified as a variable source of morbidity in different upper GI conditions [88] while *Fusobacterium* and bacterial vaginosis are common sources of preterm labour [30,31,89]. The precise biology and epidemiology of many of these infections are not clear. Unrecognized injuries to their autonomic nervous system then these may contribute, in part, to diminished host resistance and the increasing epidemics of infectious diseases and associated conditions.

Prevention of autonomic denervation and Western diseases

Earlier generations of gynaecologists were in no doubt about the direct relationships between intrapartum care and subsequent gynaecological outcomes [90-95]. Injuries to muscles and ligaments in the antero-posterior axis of the pelvis result in urinary stress incontinence and genital prolapse [96]. Intrapartum injuries to autonomic nerves in the transverse axis of the pelvis resulting in other gynaecological presentations are more recent observations [12]. Prospective, unpublished studies confirm high rates of gynaecological problems at 4 years follow-up in 2240 nulliparous women who experienced different problems in labour. Prolonged maternal voluntary efforts, operative vaginal delivery, increasing birth weight, and, increased length of the second stage of labour contribute to this morbidity. In non-Western childbirth, women labour spontaneously in the erect position and adopt the squatting position for delivery [97,98]. At present the arguments in Western childbirth polarise around the merits of "medicalised" vs. "natural" childbirth; both may contribute to unnecessary gynaecological morbidity [12,99,100]. Preventing injuries to autonomic nerves will require improved levels of maternal physical fitness, fewer medical interventions, standing in labour and squatting for delivery, and, limited maternal voluntary efforts in the second stage of labour. That is to say, management of childbirth that builds on low rates of maternal and neonatal mortality but is sensitive to the risks of unrecognized, maternal morbidity.

Breastfeeding protects infants and neonates from many clinical conditions though the mechanisms are not always apparent, e.g. T1DM, acute lymphoblastic leukaemia, asthma, etc. [101]. In non-Western communities breastfeeding is still relatively common. Bottle-feeding, or early weaning of the neonate, causes an increased frequency of infant

bowel problems include constipation and diarrhoea [102]. Breastfeeding may avoid these bowel disturbances and prevent any risk of overt, or latent, injury to autonomic nerves. On present evidence the World Health Organisation advocates 6 months of exclusive breastfeeding for all newborns [103]. Sir W. Arbuthnot Lane set out the subtle physical signs, and dire consequences, of persistent physical efforts during defaecation in the early years of the twentieth century [104–106]. The relationships between Western diets and chronic Western diseases appeared in a later era [1,2]. Excess dietary intake with limited patterns of exercise result in obesity which, allied to disordered posture and gait create pandemics of metabolic and musculoskeletal disease, though without engaging injuries to autonomic nerves. Recent studies confirm that reverting to an unrefined, low-calorie, plant-based diet results in marked improvements in cardiovascular, metabolic, malignant and other Western diseases [107–115]. Improving the quality of our diet and bowel habit is a substantial task attracting the attention of few policy-makers [116].

Conclusions

Injuries to complex and varied pathways of autonomic nerves, contribute to different phenotypes of chronic Western disease. Evidence that persistent physical efforts during defaecation and childbirth cause injuries to branches of the hypogastric plexus leading to gynaecological disease, is well established. Evidence for the cardiac and coeliac plexi in the thorax and abdomen respectively, is wide-ranging though less well supported. Diverse and cumulative consequences of autonomic denervation that are susceptible to known mechanisms of autonomic dysfunction, provide potential mechanisms for a wide range of Western diseases. They provide an explanation for D.P. Burkitt's principal observations regarding Western diseases. Simple measures applied to our diets, bowel habits, childbirth, and patterns of exercise will prevent injuries to autonomic nerves and many chronic Western diseases, as well as improving "wellness" across increasing Western lifespans.

Conflicts of interest statement

None declared.

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