‘Effects of bladder distension on autonomic mechanisms after spinal cord injuries’ by L Guttmann and D Whitteridge. Spinal Injuries Centre, Ministry of Pensions’ Hospital, Stoke Mandeville, Aylesbury, and University Laboratory of Physiology, Oxford (Brain 1947; 70: 361–404).

Although reflex autonomic responses following spinal cord lesions in man have been much studied, the conclusion that these arise solely from activity of the spinal cord below the lesion seems an inadequate explanation for the generalized sweating and cardiovascular responses affecting parts not paralysed that others have already observed. (Sir Henry) Head (1861–1940) and (Dr George) Riddoch (1888–1947) noted in their paper written after the Great War (Brain 1917; 40: 188–263; and see Brain 2008; 131: 2237–39) that one patient with a complete lesion at T7 experienced localized sweating of the head and arms following bladder distension; André-Thomas ([1897–1963]: who—as with John Hugglings Jackson (1835–1911): see Brain 2011; 134: p. 2169—liked intermittently to hyphenate two of his names and eventually dropped altogether the baptismal ‘Antoine’ and ‘Henri’) elicited pilo-erector responses after stimulation above or below the lesions of wounded French soldiers; (Otfrid) Foerster (1873–1941) produced vaso-constriction in the arms or abdomen by stimulating paralysed legs and assumed the presence of an intact paramedullary afferent pathway involving the sympathetic trunk; and (Derek) Denny-Brown (1901–81) and (Edward) Graeme Robertson (1903–75) studied rhythmic activity in the colon during micturition and reciprocal effects of the bowel on the bladder. Now—having already observed flushing of the face and upper trunk with nasal congestion, sweating, bradycardia and extrasystoles in three individuals undergoing cystometrographic examination in April 1944—(Sir Ludwig) Guttmann (1899–1980) and (Professor David) Whitteridge (1912–94) systematically study the response to bladder distension in 30 soldiers suffering ‘complete transverse lesions of the spinal cord from gunshot injuries’, categorizing cases as having lesions above T5; between T6 and T10; or below that level including one with damage to the cauda equina.

Realizing that distension of a visceral organ situated in a paralysed part of the body sets up a series of autonomic cardiovascular responses in structures above the level of the spinal lesion, Guttmann and Whitteridge have assembled a research team that involves active participation of three or four observers at any one time to study, using a variety of existing techniques or apparatus designed for the purpose, sweating and pilo-erection; vasomotor responses and heat regulation; respiration, pulse rate and blood pressure; plethysmographic recordings of pulse volume and blood flow; the electrocardiogram; and awareness of sensation. Various patterns of bladder response to filling through a suprapubic catheter are noted using the tidal drainage apparatus developed by (Sir Eric) Riches (1897–1987). A patient (C.J.) with a complete spinal lesion at C8/T1 dating from 14 May 1945 shows a small hypertonic bladder that fills without any associated detrusor or urethral activity: as the pressure reaches 32 cm of water, sweating and redness of the face and neck are noticed with nasal congestion, headache, dilation of one pupil and, at 64 cm of water, respiratory difficulty and chest pain whereupon the bladder is emptied and the symptoms rapidly subside. A soldier (R.T.) suffering a complete cord lesion at T3 on 23 June 1944 has waves of increased pressure as the bladder fills indicating detrusor activity against a closed urethra: up to 50 cm of water there is sweating and vasodilatation of the face and neck, headache, nasal congestion and penile retraction; distress, slowing of the pulse, extrasystoles and respiratory difficulty occur thereafter at which point the procedure is terminated and the autonomic symptoms rapidly recover. A man (G.L.) suffering complete spinal cord injury at T4 on 31 October 1943 has a wave form detrusor response to filling but with reduction in pressure following urethral opening and partial bladder emptying (Fig. 1): he also experiences sweating and vasodilatation of the face and upper trunk (Fig. 2A–C), with headache and flexor spasms in the legs but tolerates pressures up to 82 cm of water. The pattern of redness and sweating in these patients with thoracic cord injuries is characteristic: starting at the level of the lesion, reflex sweating soon involves the face and neck with thermoregulatory anhidrosis for a few lower segments, which is invariably complete below T10.

But with mid-thoracic lesions and lesions below that level, the situation is rather different. A patient (L.S.) with a complete cord lesion at T7 from fracture dislocation of the spine shows detrusor activity with urethral voiding: reflex sweating is mainly confined to the T10/11 dermatomes, but later extends onto the paralysed legs, which exhibit reflex spasms at pressures ~50 cm of water, whereas there is complete loss of thermoregulatory sweating below the lesion. A patient (A.B.-T.) presumed to have a longitudinal cord lesion following gunshot injury on 14 November 1944, shows no detrusor activity. His legs are flaccid and his bladder tolerates an increased volume without a marked rise in pressure,
emptying by dribbling from the urethra. No reflex sweating is observed. The same is true for all patients with lesions at or below T10; and one patient (also L.S.) with a mid-thoracic lesion from a mortar bomb explosion on 3 August 1944 also has no reflex sweating despite marked detrusor activity in response to bladder filling.

Next, in order to understand these differences in reactive sweating, Guttmann and Whitteridge consider effects on body temperature, blood pressure and the pulse. All patients experiencing reflex sweating of the face and upper trunk have increased temperature above and reduced temperature below the lesion; rectal temperature is also slightly increased. In some, alterations in blood flow, due to vasodilation, are associated with increased systolic (19–250 mmHg) and diastolic (130–150 mmHg) blood pressure in the arms. Again, these features are rarely if ever seen with lesions below T10 (Fig. 3). Pulse rate falls as blood pressure rises, each showing the same latency; but heart rate reverses more rapidly than blood pressure and returns to normal over a period of 15–30 min once bladder pressure is reduced.

Alterations in the electrocardiogram and the examples of bigeminal pulse, and extrasystoles of sino-atrial or atrio-ventricular origin, are seen in patients with lesions above T10. These are attributed to the prominent U-wave especially when this occurs at an interval of 0.40–0.48 s after the preceding R-wave, or when a short R–R interval (0.35 s) triggers an extrasystole.

‘All agents which increase the negative after potential also increase the supernormal period and the tendency to show coupled beats. An increase in calcium ion concentration,
adrenaline, and even distension of the heart can all convert a normal rhythm to a pulsus bigeminus...it is clear that we have a very satisfactory explanation for the occurrence of these coupled rhythms.'

Dr Guttmann indicates that he will soon be publishing observations correlating a transient increase in heart shadow by several centimetres during bladder distension. Although these autonomic features are potentially confounded by the profuse sweating and loss of heat through evaporation with consequent cardiovascular effects, plethysmography confirms the combination of vasodilatation in the fingers with vasoconstriction in the toes following bladder distension in the context of mid-thoracic lesions. 'When we have looked for pilo-erection, as a spinal reflex, we have always found it to accompany vasoconstriction...producing a wave of goose skin over the abdomen, trunk and the arms at the same time'. With lesions that are higher, the changes in blood flow oscillate rapidly: the common pattern is reduction in the fingers due to vasoconstriction, as the pulse rate falls and blood pressure rises but changing thereafter to vasodilatation in the upper limb with persistent vasoconstriction in the toes as the cardiovascular responses reverse. Due to its greater capacity for distension, expanding the rectum with air produces evanescent results; but the syndrome of flushing, sweating and headache has been seen by Dr Guttmann in patients with high lesions suffering visible gastric distension and peristalsis, making it 'probable that distension of many parts of the gastro-intestinal tract can give rise to reflex vasoconstriction and the whole ensuing syndrome'.

Although the modern reader may have some difficulty in categorizing the autonomic features that Guttmann and Whitteridge observe in patients classified as having high, mid-thoracic or lower lesions, and noting that these cases were seldom explored surgically so that the completeness or otherwise of the lesions was assumed but not established, the authors conclude that:

'in the context of spinal cord injury there is an opportunity to study a purely spinal viscero-cutaneous vasoconstrictor reflex elicited by distension of a viscus, devoid of any modification from higher centres ...the similarity in the behaviour of patients with spinal lesions at corresponding levels is indeed remarkable.'

The key physiological response is the relationship between blood and bladder pressure rather than vesical volume; and their interpretation is that 'in all patients with transections above L1, whose isolated cord has survived, vasoconstriction of the toes, and we feel that vasoconstriction, not limited to the skin, and mediated by the lowest parts of the sympathetic outflow, is the basic reflex response'. This can be considered part of an 'alarm' response that may be regional and confined to one part of a dermatome, thus explaining the reaction of circumscribed areas of sweating as part of the visceral-sudoral reflex that Dr Guttmann has already described. The most noticeable features—sweating, redness and the associated autonomic responses—develop over time in the unaffected parts of the body, mediated by pathways within the intact parts of the CNS. These are secondary and strictly

Figure 3 The relation between blood pressure changes and the level of the lesion. Open circle indicates systolic blood pressure before distension of the bladder. Filled circle indicates systolic blood pressure during distension of the bladder.
compensatory. This explains the vasodilation observed in patients with middle and lower thoracic cord lesions in the upper extremities that follows reflex vasoconstriction, and which maintains blood pressure within narrow limits. Conversely, patients with high cord lesions cannot compensate in this way and their blood pressure rises. The critical level at which the upper limbs may retain sufficient autonomic innervation to produce these compensatory changes is T4. At or above that level, the fingers participate in the generalized vasoconstriction and rise in blood pressure and cannot compensate; with lesions at T6/7 or below the reflex response is over-ridden by the compensatory vasodilatation from higher centres acting through the intact spinal cord. Perhaps, there is also a contribution to lowering the reflex rise in blood pressure due to the vasoconstriction reflex from dilatation of the splanchnic bed; certainly, alterations only in blood vessels of the face and neck would be insufficient to overcome the generalized rise in blood pressure. In the interests of safety, the authors have resisted the temptation to advance their physiological understanding by showing that the reduction in pulse rate, contributing to the fall in blood pressure, can be inhibited with atropine—‘this slowing was the last defensive mechanisms remaining under the control of the vasomotor centre and its elimination was unjustifiable’. As for the neurological basis, since some receptors in the bladder wall adjust to stretch while unmyelinated fibres in the

Figure 4 Complete lesion at C6 (W.B.). The effect of distension of the bladder on pulse volume, blood flow and skin temperature of the fingers just above and below the level of the lesion. The thumb has normal sensory innervations, the little finger is anaesthetic. BPS = systolic blood pressure; BPD = diastolic blood pressure; PR = pulse rate; Bl P = bladder pressure; Bl V = bladder volume; LF1 = temperature in left thumb; Ln = temperature of left side of neck; LF5 = temperature of left little finger; RF1 = filled circle: pulse volume of right thumb; RF5 = filled circle: pulse volume of right little finger; RF5 = open circle: blood flow in right little finger.
hypogastric nerve continue to discharge irrespective of the duration of stimulus, the authors conclude that the reflex effects they observe originate in the hypogastric nerve. Any role for release of adrenaline contributing to the reflex vasoconstriction seems improbable given the regional distribution of secondary vasodilation that would not escape a powerful circulating vasconstrictive factor. The nasal congestion reflects vasodilation: a striking example is provided by a patient seen within 6 h of cord transection at C4 who had bilateral Horner’s syndrome, dilated sclera vessels and complete blockage of the nasal airways so that he was gasping through a widely open mouth.

Rather striking, in understanding the compensatory dilatation of those parts that remain innervated, are cases with lesions at C7 (e.g. W.B.; see Fig 4) in which the thumb, which retains sensation, is 2–3°C warmer than the anaesthetic little finger. The pattern of sweating in response to bladder distension—extensive in the face and upper trunk in high cord lesions but less marked with mid-thoracic injury—suggests that distribution of the sudomotor response depends on the distance of the spinal lesion from the cervicothoracic and thoracico–lumbar regions, respectively. Parts nearest to the lesion show especially marked irritability and an exaggerated response to stimulus: ‘this would explain the band-like area of hyperhidrosis in restricted dermatomes’. Sweating cannot be attributed to activity of fibres arising from the spinal cord below the lesion; it must be part of the thermoregulatory response mediated by efferent fibres arising from above the lesion. Dr Guttmann is impressed by patients who have observed for themselves the connection between bladder pressure and cardiovascular responses: one intelligent officer knew that his bladder was full simply because his heart started to pound and beat slowly; a patient of Professor (Jacques Jean) Lhermitte (1877–1959) expected his bladder to empty soon after his ears went red. And in the recent Paralympic Games (see page 3193), informed athletes—evidently up to speed in physiology—might occasionally be observed applying intense lower abdominal pressure to their full bladders, as the official reached for the starter’s gun!

‘These observations have emphasised the importance of the role of the nervous system in the maintenance of a stable internal environment. After complete lesion of the spinal cord, this regulatory function becomes increasingly deficient the higher the lesion of the spinal cord. In particular, the failure to regulate blood pressure, blood-flow and body temperature is not only responsible for imposing limitations on the activity of a paraplegic, but also results in the development of widespread abnormal reactions of autonomic mechanisms to visceral activity in the paralysed parts of the body. Certain components of the autonomic reflex responses occurring above the level of the lesion, such as flushing, sweating in the face and neck, blockage of nasal air passage, and headaches, represent alarm symptoms indicating abnormal activity of a viscus in the anaesthetic area below the level of the lesion. Their correct recognition by medical and nursing staff is an important guide for immediate and appropriate action.’

With lesions above L2 bladder distension leads to vasoconstriction of the toes; when the lesion is between L2 and T6, this is followed by vasodilatation in the fingers; above T5, the vasoconstriction is not compensated other than in the face and nasal mucosa, and blood pressure rises, the pulse droops, cardiac rhythm disturbances are likely, and the patient sweats.

With David Whitteridge, Ludwig Guttmann described physiological responses to bladder distension. He understood the importance of limiting bladder infection but his only option was regular sterile catheterization and bladder washouts, together with penicillin smuggled in from Oxford. He changed the prognosis following spinal cord injury. As the paper from Vieri Failli and colleagues in the current issue on the role of systemic infections in orchestrating the prognosis after spinal cord injury makes clear (page 3238), Guttmann’s patients adjusted to their disabilities but they did not recover; nor does the patient with severe spinal cord injury in 2012. But knowledge on the neurobiology of regeneration in the CNS moves on, and the present issue contains an encouraging account of recovery following transplantation of stem cells (page 3227). The ‘patients’ are dogs managed by Nicolas Granger and a team working in veterinary surgery, but the implications for bipedal victims of spinal cord injury are clear.

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