

INVITED REVIEW

Neurological disorders of micturition and their treatment

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Summary

An overview of the current concepts of the neurological control of the bladder is given, based on laboratory experiments and PET scanning studies in human subjects. This is followed by a description of the various causes of the neurogenic bladder, discussed in a hierarchical order starting with cortical lesions and descending through the basal ganglia and brainstem, spinal cord, conus and

cauda equina to disorders of peripheral innervation. Then follows a description of the condition of isolated urinary retention in young women. The article concludes with a review of the methods available for treating neurogenic bladder disorders. These are largely medical but brief mention of appropriate surgical procedures is made.

Keywords: neurogenic bladder; detrusor hyperreflexia; incontinence; urinary retention

Abbreviations: CRD = complex repetitive discharge; CVA = cerebrovascular accident; DDVAP = desmopressin; MSA = multiple system atrophy; SPECT = single photon emission computed tomography

Introduction

Some knowledge of the neurophysiological control of the bladder is essential to understand the many and various urinary complaints that can arise as a result of neurological disease. The bladder performs only two functions—storage and emptying. The modern view of the control of these two mutually exclusive activities is that neural programs to perform each exist in the pons and that suprapontine influences act to switch from one state to the other. Micturition frequency in a healthy adult with a bladder capacity of ~500 ml is likely to be about once every 3–4 h, depending on fluid intake. Since the act of voiding lasts 2–3 min, this means that for >98% of life the bladder is in its storage mode.

In health and continence the decision when to void is determined by the perceived state of bladder fullness together with an assessment of the social appropriateness to do so. To effect both storage and voiding, connections between the pons and the sacral spinal cord must be intact as well as the peripheral innervation which arises from the most caudal segments of the sacral cord. From there the peripheral innervation passes through the cauda equina to the sacral plexus and via the pelvic and pudendal nerves to innervate the bladder and sphincter. Thus, the innervation needed

for physiological bladder control is extensive, requiring suprapontine inputs, intact spinal connections between the pons and the sacral cord, as well as intact peripheral nerves. Urinary continence is a severe test of neurological integrity: a fact that has been recognized ever since neurology texts were written. Some of the great neurologists and neuroscientists at the turn of the century were interested in the neurology of bladder control and the book by Becterev *On Fundamentals of Brain Function* (in Russian, 1903) includes a chapter on this topic. L. R. Müller after observing Victor Horsley performing human spinal surgery, carried out experiments on dogs' lower spinal cord to observe bladder function (Neundorfer and Hilz, 1998) and was greatly interested in clinical aspects of the neurogenic bladder (Müller, 1920).

Neurophysiological control of the bladder—animal experiments

In the 1920s, Barrington, working on decerebrate cats at University College Hospital, London, demonstrated that the 'middle pons was the level in the brain at which the motor tone of the bladder arises' (Barrington, 1921). Some 40 years

later Kuru carried out further studies in cats and suggested that the group of cells in the pons which when electrically stimulated resulted in a detrusor contraction be called 'Barrington's nucleus' (Kuru and Yamamoto, 1964). Subsequent studies by de Groat's group (de Groat, 1975; Noto *et al.*, 1991) and later Holstege's group refined details of the brainstem activity involved in bladder storage and voiding in animals (Holstege *et al.*, 1979, 1986; Griffiths *et al.*, 1990). Stimulation of a medial region in the dorsum of the pons results in an immediate decrease in urethral pressure and silence of pelvic floor EMG signal, followed by a rise in detrusor pressure. This region which Holstege and colleagues called the 'M-region' (medial) is the same area as the pontine micturition centre or Barrington's nucleus. Tracing studies demonstrated direct projections from the 'M-region' to the intermediolateral cell column of the sacral cord and the parasympathetic preganglionic bladder motor neurons in the cat (Blok and Holstege, 1997). Stimulation of a nucleus at the same level of the pons but more laterally placed, the so-called 'L-region' (lateral), results in a powerful contraction of the urethral sphincter (Holstege *et al.*, 1986). Injection of radioactive leucine into the 'L-region' produced labelled fibres in Onuf's nucleus (Holstege *et al.*, 1986) which is the motor nucleus containing the anterior horn cells innervating the sphincters. It was therefore proposed that the 'L-region' be regarded as important for continence and 'M-region' the site of activation for micturition (Griffiths *et al.*, 1990).

A brainstem mechanism whereby the bladder is 'switched' from one mode of activity to the other is now generally accepted in experimental animals and, as a result of the PET scanning studies also in humans. However, there are a number of other segmental reflexes controlling bladder and sphincter behaviour which have been identified in experimental animals; the importance and relevance of these to humans is uncertain. The control of the bladder in newborn kittens, rat pups, etc. is quite different from that in adult animals, and it seems likely that, although various sacral segmental reflexes may be of functional significance in infancy, with maturation pontine and supra-pontine mechanisms become the controlling influence. However, in pathological states these 'primitive' or infantile reflexes may re-emerge and in humans become clinically relevant. Most important in this respect is the C-fibre mediated reflex which emerges following disconnection from pontine regulatory influences as a consequence of spinal cord disease. The undesirable clinical effects of this may be alleviated by intravesical capsaicinoids.

Studies in humans of the neural control of bladder function

The recent publication of PET studies in male and female subjects of voiding have demonstrated that the neurological control of the bladder in man is essentially similar to that which had been demonstrated in experimental animals (Blok

et al., 1997, 1998). Right-handed volunteers were trained to void whilst lying in the scanner, but in both studies a proportion of both the male and female subjects were unable to do this. The differences seen between the 'successful' and 'unsuccessful' voiders were of great interest. Focusing on the dorsomedial tegmentum of the pons it was shown that in successful voiders there was activity in a region of the medio-posterior pons and it was suggested that this is the human homologue of the so called 'M-region' in animals (Blok and Holstege, 1994). In the 'unsuccessful' voiders, during the time when the subjects were attempting to void but failing, a region in the ventrolateral pontine tegmentum was seen to be activated (Fig. 1). It was proposed that this is the region homologous to the 'L-region' of the cat.

In the cerebral cortex there was significant activity in the right inferior frontal gyrus and the right anterior cingulate gyrus during voiding which was not present during the withholding phase. This area of the cortex is thought to be involved in the performance of intended actions about which a planned decision has to be made. A significant difference was also seen in the right cingulate gyrus, this being activated more in the posterior and superior region during voiding, but reduced during withholding of voiding. The significance of this is thought to be that this area is involved in alertness—it is an area which is activated if an action is facilitated and reduced if there is inhibition of an activity (Blok *et al.*, 1997).

A report had been published a few months earlier from a group in Japan who had used single proton emission computed tomography (SPECT) to study micturition (Fukuyama *et al.*, 1996). However, whereas the PET studies looked at the initiation of micturition, the protocol used in the SPECT study examined the later phases of sustained micturition. On the basis of increased cerebral blood flow during voiding compared with that of the resting state, small areas in the midpons extending into the midbrain, the left sensorimotor cortex, the right lateral frontal cortex and bilateral supplementary motor areas were thought to be activated by the process of bladder emptying. The ponto-midbrain area which enhanced during micturition was thought to be in the region of the periaqueduct grey matter, a region which had been shown to be acting as a sensory-integration relay centre for micturition in animals (Blok and Holstege, 1994).

Although the PET studies (Blok *et al.*, 1997, 1998) showed pronounced right-sided involvement in control of bladder function, the authors advised caution in assuming significant lateralization since in the experimental cat, bilateral pontine lesions are necessary before an effect is noticed.

Frontal lobe lesions and bladder control

Prior to the findings of these functional brain imaging experiments in humans, all that was known about the cortical control of the bladder was based on clinical studies of patients with brain lesions. The most influential study was that by Andrew and Nathan (Andrew and Nathan, 1964) in which those authors described 38 patients who had disturbances of

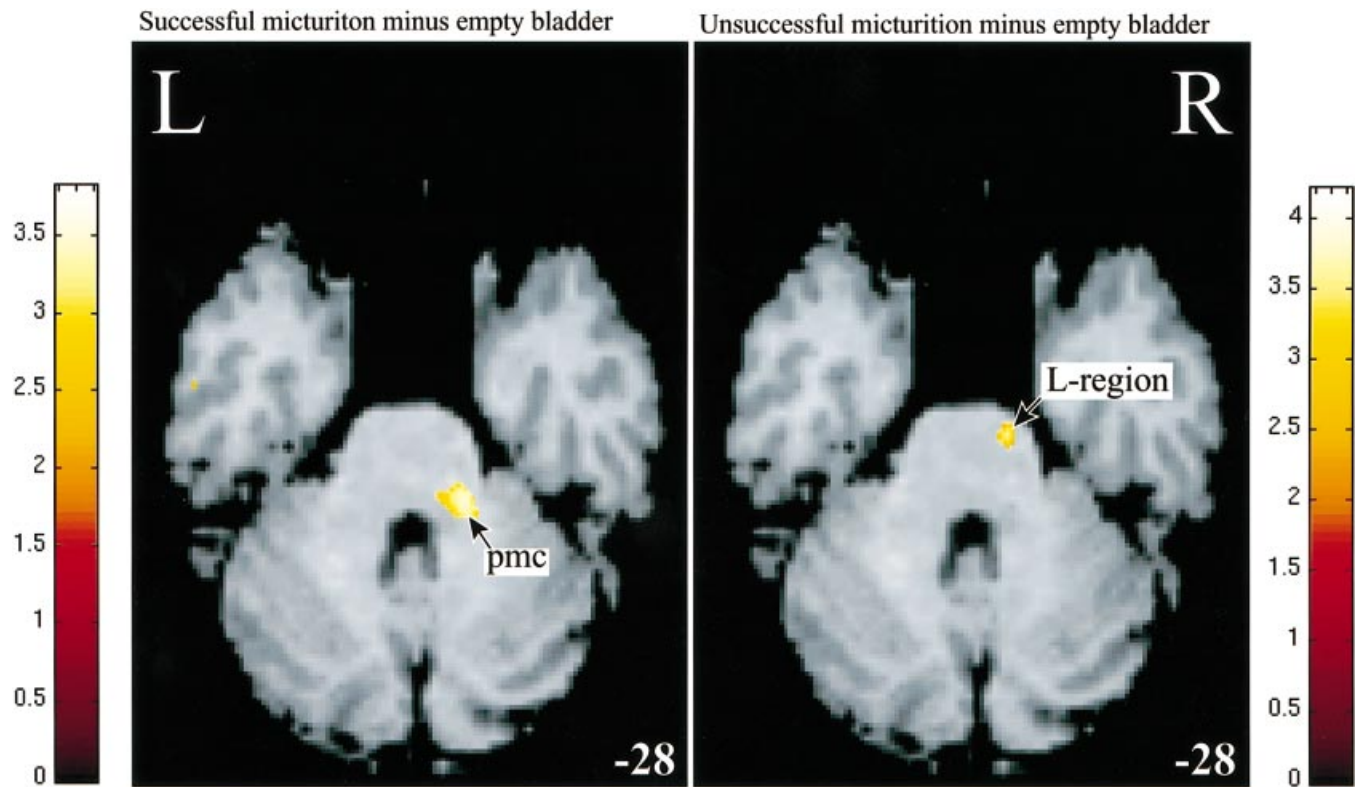


Fig. 1 Brainstem activation in women who could (*left*) and could not void (*right*). The number -28 refers to the distance in millimetres relative to the horizontal plane through the anterior and posterior commissures (z -direction). The numbers on the colour scale refer to the corresponding Z-scores (significance); pmc = positive micturition centre. From Blok *et al.* (Blok *et al.*, 1998) with permission from the editor.

micturition resulting from lesions in the anterior frontal lobe. In their series there were 10 patients with intracranial tumours, two with anterior frontal lobe damage following rupture of an aneurysm, four who had penetrating brain wounds and 22 patients who had undergone leucotomy. The authors explain that the leucotomy cases were the most useful in terms of localization of the important brain structures and from study of these patients the authors concluded that the area shown in Fig. 2 was critical for bladder control.

The typical clinical picture of frontal lobe incontinence they described was of a patient with severe urgency and frequency of micturition and urge incontinence, without dementia, the patient being socially aware and embarrassed by the incontinence. Micturition was normally co-ordinated, indicating that the disturbance was in the higher control of these processes. The infrequency with which such patients are encountered is stressed by the authors, explaining that they had each been collecting cases separately over a period of 24 years and only just prior to writing did they learn of each other's interest and combine to present a joint paper (Andrew and Nathan, 1964).

Two years later Andrew and colleagues (Andrew *et al.*, 1966) described six cases with disturbances of micturition due to aneurysms of anterior communicating or anterior cerebral arteries. In this paper they reviewed the animal experimentation literature on neurological bladder control

and hypothesized that it was the disconnection of the frontal or anterior cingulate regions from the septal and hypothalamic areas which allowed micturition to proceed automatically and involuntarily following brain damage.

Although the 1964 paper by Andrew and Nathan has been the most influential in the study of frontal lobe control of the bladder, it was not in fact the first. In 1960 Ueki had published a paper which Andrew and Nathan were unaware of at the time they were writing (Ueki, 1960). Ueki, a Japanese neurosurgeon, had analysed the urinary symptoms of 462 patients who had come to surgery for brain tumours, 34 cases of frontal lobectomy and 16 cases of bilateral anterior cingulectomy. He illustrated his conclusions with a diagram showing a strong positive influence on micturition of an area in the pons and an inhibitory input from the frontal lobe and bilateral paracentral lobules.

In 1901 Czyhlarz and Marburg had published on this subject in German (Czyhlarz and Marburg, 1901) and this author is grateful to Dr Peter Nathan for a translated summary. The paper consists of a description of two cases identified by the authors and other cases taken from the literature. One of the inevitable defects with such a study at that time was that tumours could only be localized on clinical grounds and by the time a post-mortem was performed, the lesions responsible for the clinical condition were considerably larger and inevitably poorly localized. From the clinical evidence

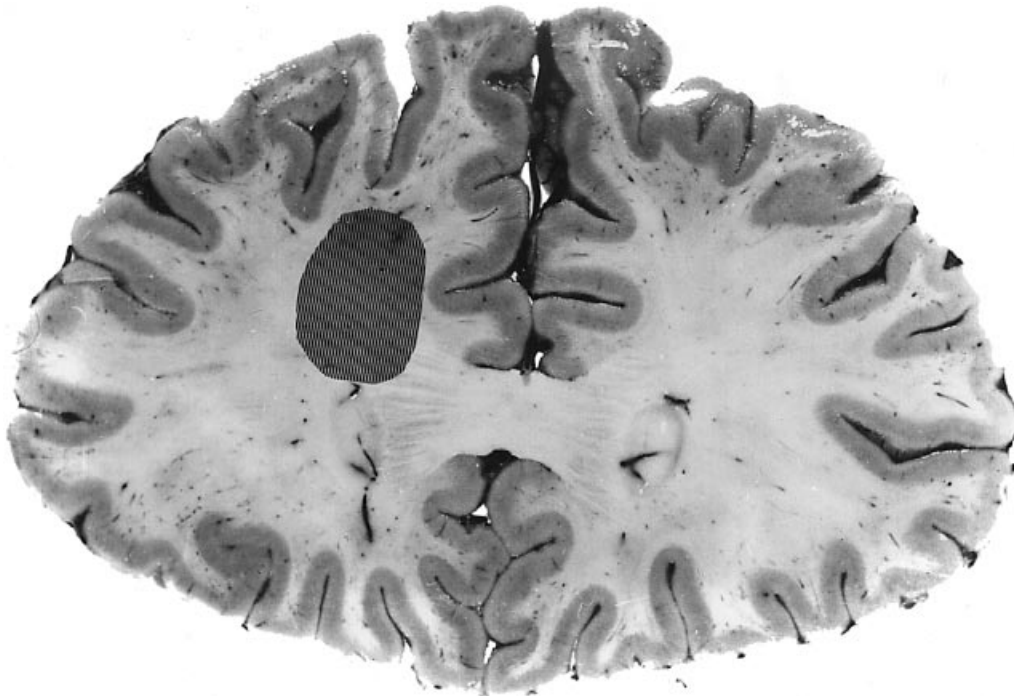


Fig. 2 Photograph of coronal section of frontal lobes with the shaded area covering the area involved in the lesions described as causing disturbances of micturition, from Andrew and Nathan (Andrew and Nathan, 1964). The plane of the section is the plane through which leucotomies were made that caused the syndrome they described.

available it was concluded that the cortical field of the bladder was in the motor zone in a region between the arm and the leg and the clinical manifestation of a disturbance in this region was difficulty initiating micturition and thus urinary retention. The author reported cases with lesions in other parts of the CNS in whom micturition was affected, and in particular lesions in the pons. Dr Nathan concludes his translation notes with the comment 'this paper was written because people did not believe that there was such a thing as cerebral disturbance of the bladder'.

Following the paper by Andrew and Nathan, Maurice-Williams reported a series of 50 consecutive cases of frontal lobe tumours and found seven patients exhibiting the syndrome previously described (Maurice-Williams, 1974). It was not found in 100 consecutive non-frontal intracranial tumours, indicating the localizing value of the syndrome. The author also observed that 'it is odd that the syndrome may be relieved by excision of both the causative lesions and the area of brain it involves' because in five of the cases resection of a tumour relieved the micturition symptoms for up to 2 years (Maurice-Williams, 1974). From this it was concluded that the phenomenon was a positive rather than negative one, the lesion activating some system rather than releasing one from control. This author also noted an apparent preponderance of right-sided tumours—six out of seven cases in his series. Another paper looking at patients with frontal lobe lesions concluded damage to the right superior prefrontal region was associated with transient incontinence, whereas

permanent incontinence was associated with bilateral damage (Mochizuki and Saito, 1990).

Urinary retention has also been described in patients with brain lesions. In the series by Andrew and Nathan, two of their patients were in urinary retention at some stage (Andrew and Nathan, 1964). More recently there have been three case histories of elderly females with various forms of right frontal lobe pathology who had urinary retention. In two, one with an abscess and the other with a haematoma, successful treatment brought recovery of bladder function (Yamamoto *et al.*, 1995; Lang *et al.*, 1996).

Bladder dysfunction studied urodynamically following cerebrovascular accidents

There have been a number of urodynamic studies of groups of patients who have had cerebrovascular accidents (CVAs) and subsequently developed urinary symptoms. The conclusions drawn from these groups of patients with disparate cortical lesions are that in general, voiding is normally co-ordinated, no patients showing evidence of detrusor sphincter dyssynergia, and that the commonest cystometric finding is detrusor hyperreflexia (Khan *et al.*, 1981; Tsuchida *et al.*, 1983; Kuroiwa *et al.*, 1987; Khan *et al.*, 1990).

Most recently Sakakibara and colleagues (Sakakibara *et al.*, 1996c) reported on the bladder symptoms of 72 patients who had been admitted with an acute hemispheric stroke. When

assessed at 3 months, 53% were found to have significant urinary complaints. The commonest problem was of nocturnal urinary frequency which affected 36%, while urge incontinence affected 29% and difficulty in voiding 25%. Urinary retention was seen in the acute phase of illness in 6%. A significant positive correlation was found between the occurrence of a urinary disturbance and hemiparesis and a negative correlation with hemianopia. Brain imaging techniques confirmed a more anterior location of brain lesions in the former group. Urodynamic studies of 22 of the symptomatic patients showed detrusor hyperreflexia in 68%, detrusor-sphincter dyssynergia in 14% and uninhibited sphincter relaxation in 36%. Patients with urinary retention had detrusor areflexia and an unrelaxing sphincter. No statistically significant correlation could be demonstrated between any particular lesion site and urodynamic findings. Although there was some indication that lesion size was related to the occurrence of urinary symptoms, a preponderance of right sided lesions was not found. The findings suggested that damage to the anteromedial frontal lobe and its descending pathway and the basal ganglia is mainly responsible for micturitional dysfunction in stroke patients.

Epidemiological studies of incontinence following CVA

Analysis of the symptoms of 532 patients seen within 7 days of their stroke found that the presence of urinary incontinence appeared to be a more powerful prognostic indicator for poor survival and eventual functional dependence than a depressed level of consciousness in this period (Wade and Hewer, 1985; Barer and Mitchell, 1989). It was suggested either incontinence was the result of a severe general rather than specific loss of function or that those who were incontinent were less motivated to recover both continence and more general function. Outcome was so much better in those who remained or became dry that it seems possible that recovery of continence may promote morale and self-esteem which can actually hasten overall recovery.

Urinary incontinence in the elderly and institutionalized

Detrusor function appears to decline with age so that there is a trend towards a reduction in strength of contraction of the detrusor and impairment of emptying efficiency leading to larger post-void residual volumes with increasing age (Malone-Lee and Wahedna, 1993). It has been proposed that these changes are due to degenerative changes in detrusor muscles with characteristic electron microscopic abnormalities (Elbadawi *et al.*, 1993) and, although debate continues as to the specificity of the ultrastructural changes described, it now seems clear that there is primary detrusor pathology with aging and not all bladder dysfunction is

secondary to cortical disease, as was once thought. The commonest demonstrable abnormality of bladder function in the institutionalized elderly is detrusor overactivity (Resnick *et al.*, 1989). The combination of involuntary detrusor contraction, i.e. detrusor hyperreflexia leading to urge incontinence together with impaired contractile function causing incomplete bladder emptying has been termed DHIC (Resnick and Yalla, 1987), but whether this is a single condition or due to the ageing detrusor malfunction occurring in combination with cortical dysfunction causing overactivity remains the subject of some discussion.

The cause of urinary incontinence in dementia is probably multi-factorial. Not all incontinent elderly are cognitively impaired, nor are all cognitively impaired elderly incontinent. A study which looked at the association between cognitive impairment and bladder dysfunction concluded that urge incontinence and reduced bladder sensation were associated with reduced frontal lobe perfusion on SPECT brain imaging (Griffiths *et al.*, 1994). In a study of patients with cognitive decline, incontinence was associated with severe mental failure in pure Alzheimer's disease, but preceded by severe cognitive impairment in diffuse Lewy body disease (Del-Ser *et al.*, 1996). A much less common cause of dementia, low-pressure hydrocephalus has incontinence as a cardinal feature (Hakim and Adams, 1965) and improvement in urodynamic function has been demonstrated within hours of lumbar puncture in patients with this disorder (Ahlberg *et al.*, 1988).

Thus, in addition to the various possible neurogenic causes of impaired bladder control and the contribution of abnormal detrusor behaviour in the elderly, the existence of concomitant urological disorders should be considered in each patient. Urinary incontinence in an elderly person is likely to be a complex problem and it is often the onset of incontinence which leads to institutionalization. The scale of the problem has significant socio-economic consequences and the cost of containment of incontinence forms a significant proportion of the national budget for healthcare in countries with advanced medicine (Royal College of Physicians, 1995).

Bladder symptoms in patients with parkinsonism

Although the basal ganglia have been shown to have an effect on micturition reflexes in experimental animals, there are several possible causes of urinary symptoms in a patient with parkinsonism. These include a number of possible neurogenic causes depending on the exact underlying neurological diagnosis as well as local urological problems. In Parkinson's disease bladder symptoms usually occur at an advanced stage of the disease and prostatic outflow obstruction should first be excluded in an elderly man. However, in a patient with severe urinary symptoms yet relatively mild parkinsonism a diagnosis of multiple system atrophy (MSA) should be considered.

The onset of urogenital symptoms in MSA may precede

Table 1 Urogenital criteria which favour a diagnosis of multiple system atrophy

Urinary symptoms preceding or presenting with parkinsonism
Urinary incontinence
Post-micturition residual volume >100 ml
Erectile dysfunction preceding or presenting with parkinsonism
Worsening bladder control after urological surgery

overt neurological involvement by some years and in a study of the duration of symptoms, erectile dysfunction and bladder complaints began 4–5 years prior to the diagnosis and, on average, 2 years before more specific neurological symptoms appeared. Almost half the male patients had had a transurethral prostatectomy with a beneficial result in very few (Beck *et al.*, 1994).

The neuronal atrophy process of MSA probably affects the CNS at several different locations which are important for bladder control, explaining why urinary complaints occur early and are so severe. It has been suggested that detrusor hyperreflexia is due to cell loss in the brainstem region, whereas incomplete bladder emptying is due to loss of parasympathetic drive on the detrusor following atrophy of cells in the intermediolateral cell columns (Kirby *et al.*, 1986). In addition, anterior horn cell loss in Onuf's nucleus (Sung *et al.*, 1979) results in denervation of the urethral sphincter so that the patient has a combination of bladder overactivity, together with incomplete emptying and a weak sphincter. There may be a marked clinical change in bladder dysfunction during the progression of MSA. Although patients often present with detrusor hyperreflexia, over the course of ensuing months or years a failure of bladder emptying may develop so that the post-micturition residual volume increases (Sakakibara *et al.*, 1993b).

Because of the motor neuron loss in Onuf's nucleus, changes of chronic reinnervation in the motor units of both sphincters may be demonstrated and sphincter EMG may be contributory in making the diagnosis (Pramstaller *et al.*, 1995; Palace *et al.*, 1997). However, if this test is not available there are clinical urological criteria which may assist in recognizing patients with MSA (Table 1) and should make a urological surgeon cautious about operating (Chandiramani *et al.*, 1997).

Bladder symptoms in other parkinsonian syndromes are less prominent (Sakakibara *et al.*, 1993a) and, although they may occur as part of the patient's general disability, are rarely so severe or occur at a stage of the disease when a neurological pathogenesis is not evident so that urological surgery might be considered.

In patients with Parkinson's disease and bladder symptoms, there may be considerable difficulties in establishing the exact cause, and treatment is often problematic. Typically patients present at an advanced stage of the neurological disease. The bladder symptoms usually come on after many years of treatment for Parkinson's disease (Chandiramani *et al.*, 1997) and patients often show features of the long-

term side-effects of levodopa. They complain of urgency, frequency and sometimes urge incontinence. Urodynamic studies in series of patients with Parkinson's disease have found that the commonest urodynamic abnormality is detrusor hyperreflexia (Pavlakis *et al.*, 1983a; Fitzmaurice *et al.*, 1985; Berger *et al.*, 1987; Christmas *et al.*, 1988; Hattori *et al.*, 1992; Aranda and Cramer, 1993) and there are several possible causes for this. The hypothesis which has been most widely proposed is that in health the basal ganglia have an inhibitory effect on the micturition reflex, and with cell loss in the substantia nigra, detrusor hyperreflexia develops. There is experimental data to support this since marmosets with MPTP (1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine) induced parkinsonism were found to have detrusor hyperreflexia (Albanese *et al.*, 1988) and stimulation of the substantia nigra in cat experiments inhibited distention induced rhythmical contractions of the bladder (Lewin *et al.*, 1967; Yoshimura *et al.*, 1992). Further studies on anaesthetized cats demonstrated that rhythmic contractions were inhibited by intracerebroventricular administration of a D1 receptor agonist but were not affected by a D2 receptor agonist (Yoshimura *et al.*, 1992). From this it was concluded that the dopamine D1 receptor is the main inhibitory influence on the micturition reflex in the cat and studies in the MPTP treated marmoset confirmed the same was true for the primate model (Yoshimura *et al.*, 1993).

The results of clinical studies which have looked at the effect of L-dopa or apomorphine on bladder behaviour in patients with Parkinson's disease have been conflicting. In patients showing 'on-off' phenomena cystometry done in both states showed a lessening of hyperreflexia with L-dopa in some patients and a worsening in others (Fitzmaurice *et al.*, 1985). A similar unpredictable effect was found on detrusor hyperreflexia when subcutaneous apomorphine was given in one study (Christmas *et al.*, 1988), although in another all those with detrusor hyperreflexia improved (Aranda and Cramer, 1993). From the animal studies it would seem sensible to treat patients with bladder symptoms with a D1 receptor agonist, and pergolide with its dual D1 and D2 receptors activity has been tried in patients with Parkinson's disease and bladder symptoms. A significant improvement both symptomatically and urodynamically was reported in a small series of patients (Yamamoto, 1997).

Although the hypothesis that bladder dysfunction is due primarily to basal ganglia disease is generally accepted there are other factors which should be considered. A potentially correctable cause such as prostatic outflow obstruction should be considered in an older male patient. The poor reputation for outcome following prostatic surgery that patients with Parkinson's disease have may well have been due to the inclusion of patients with MSA in the studies of 'Parkinson's disease and the bladder' (Berger *et al.*, 1987; Staskin *et al.*, 1988). However, most publications of this decade recognize the potential problem and give some statement about the certainty of neurological diagnosis. If there is convincing evidence of prostatic occlusion, a prostatectomy should be

considered, bearing in mind that some men with Parkinson's disease do benefit from this operation (Staskin *et al.*, 1988; Chandiramani *et al.*, 1997).

There may also be outflow obstruction in Parkinson's disease due to impaired relaxation or 'bradykinesia' of the urethral sphincter (Galloway, 1983; Christmas *et al.*, 1988). A study in which domperidone was followed by subcutaneous apomorphine in patients with Parkinson's disease and urinary symptoms found that apomorphine reduced bladder outflow resistance and improved voiding in all 10 patients in the study (Christmas *et al.*, 1988). It was proposed that this method of investigation be used to demonstrate the reversibility of outflow obstruction in men with Parkinson's disease before prostatic surgery be undertaken.

A final consideration is the possible effect of the dopaminergic medication on the detrusor muscle itself. Dopamine D1 and D2 receptors have been demonstrated in bladder biopsies using radioligand binding and autoradiographic techniques (Escaf *et al.*, 1994), but the long-term effect on these receptors of exposure to L-dopa is not known.

Bladder dysfunction and brainstem lesions

In 1926 Holman noted that voiding difficulty could be a sign of posterior fossa tumours (Holman, 1926) and in the series of patients with brain tumours voiding difficulty was reported to occur in 46 (30%) out of 152 patients with posterior fossa tumours while urinary incontinence occurred in only 3 (1.9%; Ueki, 1960). Renier and Gabreels (Renier and Gabreels, 1980) found urinary retention in 12 out of 17 children with pontine glioma. There have also been a number of case histories of patients presenting with difficulty with micturition and various brainstem pathologies (Betts *et al.*, 1992; Manente *et al.*, 1996; Sakakibara *et al.*, 1998).

Sakakibara and colleagues (Sakakibara *et al.*, 1996d) reported the urinary symptoms of 39 patients who had had brainstem strokes. Almost half the patients had urinary symptoms, nocturnal urinary frequency and voiding difficulty in 28%, urinary retention in 21% and urinary incontinence in 8%. The problems were more common following haemorrhage, probably because the damage was usually bilateral. Urinary symptoms did not occur in those with lesions of midbrain, but it did in 35% of those with pontine lesions and 18% with medullary stroke. A correlation was found between urinary symptoms and sensory disturbance, abnormal eye movement and with inco-ordination. Urodynamic studies in 11 symptomatic patients showed detrusor hyperreflexia in eight (73%), low compliance bladder in one (9%), detrusor areflexia in three (27%; 3 months, 6 months and 3 years after the occurrence, respectively), non-relaxing sphincter on voiding in five (45%) and uninhibited sphincter relaxation in three (27%). The proximity of the medial longitudinal fasciculus to the presumed pontine micturition centre in the dorsal pons means that a disorder of eye movement such as an internuclear ophthalmoplegia is

highly likely in patients with pontine pathology causing a voiding disorder.

Pathophysiological consequences of spinal cord disease for bladder function

Trans-spinal pathways connect the pontine micturition centres to the sacral cord and intact connections are necessary to effect the reciprocal activity of the detrusor and sphincter needed to 'switch' between storage and voiding. Following disconnection from the pons this synergistic activity is lost and the result is that the sphincter tends to contract when the detrusor is contracting, a condition known as 'detrusor-sphincter dyssynergia'. In addition new reflexes emerge to drive bladder emptying and cause detrusor hyperreflexia. Immediately following spinal cord transection and during the phase of spinal shock, the bladder is acontractile but gradually over the course of some weeks, reflex detrusor contractions develop in response to low volumes of filling. The neurophysiology of this recovery has been studied in the cat and it has been proposed that following spinal injury and damage to the pontine micturition centre, C fibres emerge as the major afferents forming a spinal segmental reflex which results in automatic voiding (Thor *et al.*, 1986; de Groat, 1990). It is assumed that the same pathophysiology occurs in man and the response to intravesical capsaicin (a C fibre neurotoxin) of patients following acute traumatic spinal cord injury (Wiert *et al.*, 1998) or the chronically progressive spinal cord disease multiple sclerosis suggests this may be the case (Fowler *et al.*, 1994).

The abnormally overactive small capacity bladder which characterizes spinal cord disease means that patients are troubled by urgency and frequency, and if the detrusor hyperreflexia is severe and particularly if there is also a spastic paraparesis, urge incontinence is likely since impaired mobility may contribute to difficulty in reaching the toilet in time.

Poor neural drive on the detrusor muscle during attempts to void (Mayo and Chetner, 1992) together with an element of detrusor-sphincter dyssynergia means that there is likely to be incomplete bladder emptying and this may in turn exacerbate the symptoms due to detrusor hyperreflexia. Although the neurological process of voiding may have been equally severely disrupted by spinal cord disease as the process of storage, the symptoms of difficulty emptying may be relatively minor compared with those of urge incontinence. It may be that it is only on direct questioning that a patient will admit to difficulty initiating micturition or an interrupted stream, or possibly a sensation of incomplete emptying (Betts *et al.*, 1993).

A valuable clinical point is that, because the innervation of the bladder arises more caudally than the innervation of the lower limbs, any form of spinal cord disease which causes bladder dysfunction is likely to produce clinical signs in the lower limbs, unless the lesion is completely restricted

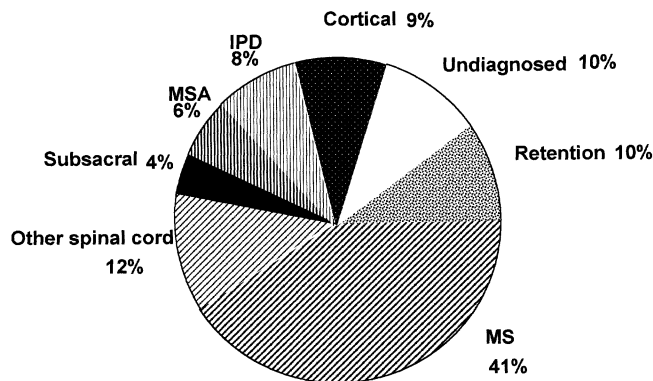


Fig. 3 Pie chart showing underlying neurological problems of 140 patients presenting over a 12-week period with bladder symptoms. IPD = idiopathic Parkinson's disease; MSA = multiple system atrophy; subsacral = cauda equina; MS = multiple sclerosis.

to the conus. Indeed this is a sufficiently reliable rule to be of great value when considering whether or not a patient has a neurogenic bladder due to spinal cord involvement.

Figure 3 shows the results of an unpublished study of the neurological cause of bladder symptoms in patients attending the Department of Uro-Neurology at The National Hospital, Queen Square over a period of 12 weeks. Given that the site of responsible pathology in multiple sclerosis is spinal (Betts *et al.*, 1993), the diagram shows that spinal cord disease was responsible for bladder dysfunction in almost half the patients. This conclusion is borne out by a study of the urinary complaints of 786 patients with neurological disorders consecutively admitted to hospitals in Catania, Sicily. Fifty-six percent had bladder symptoms and in 10% these were thought to be urological. Of the 438 patients with neurogenic bladder dysfunction, 74% had some form of spinal cord disease (Ventimiglia *et al.*, 1998).

Spinal cord injury

Much has been written about the urological aspects of bladder dysfunction following spinal cord injury. Detrusor hyperreflexia, loss of compliance and detrusor-sphincter dyssynergia that occur as a consequence of spinal cord injury can be of such severity as to cause ureteric reflux, hydronephrosis and eventual upper renal tract damage. Before the introduction of modern treatments, renal failure was a common cause of death following spinal cord injury. The bladder problems of those with spinal cord injury must therefore be managed in such a way as to lessen the possibility of upper urinary tract disease as well as provide the patient with adequate bladder control for a fully rehabilitated life. Those with spinal cord injury are often young and otherwise fit and it may be better for them to undergo surgery on their lower urinary tract with a view to fulfilling these two aims of management rather than be managed by the medical means which are most suitable for patients with progressive neurological disease.

Progressive spinal cord disease and bladder dysfunction

The pathophysiological consequences of progressive neurological disease affecting the spinal cord are similar to those of spinal cord injury, but the medical context of increasing disability is such that the patient's management must be quite different. There is likely to be general neurological involvement which must be considered together with impaired bladder function. Multiple sclerosis is the commonest example of the problem.

Multiple sclerosis

In patients with multiple sclerosis there is a strong association between bladder symptoms and the presence of clinical spinal cord involvement including paraparesis and upper motor neuron signs on examination of the lower limb (Betts *et al.*, 1993). Both clinical studies and more recently MRI studies have shown that ~75% of those with a diagnosis of multiple sclerosis have spinal cord involvement (Kidd *et al.*, 1993). The estimated incidence of bladder dysfunction in multiple sclerosis is similar (Miller *et al.*, 1965).

The commonest urinary symptom that patients with multiple sclerosis complain of is urgency. All series of urodynamic studies of patients with multiple sclerosis have shown that this is due to underlying detrusor hyperreflexia (Chancellor and Blaivas, 1995). Urge incontinence is likely to be a problem if the patient also has impaired mobility and this together with frequency means that many patients are reluctant to be far away from access to a toilet. The symptoms of impaired voiding are often less prominent and may only be elicited by direct questioning. Patients may volunteer or admit on direct questioning to hesitancy of micturition, but the more disabled may find themselves unable to initiate micturition voluntarily, only emptying their bladders with an involuntary hyperreflexic contraction. In addition to hesitancy, an interrupted urinary flow pattern may be reported. Evidence of incomplete emptying may not come from a reported sensation of continued fullness after voiding, but rather the observation by the patient that having passed urine once they are able to do so again within 5–10 min (Betts *et al.*, 1993). A very similar clinical picture may be seen in adrenomyeloneuropathy (Moser *et al.*, 1991).

As the neurological condition progresses the bladder dysfunction may become more difficult to treat. This is because of worsening detrusor hyperreflexia, decreasingly efficient emptying in the context of worsening paraparesis, recurrent urinary infections, spasticity and general immobility and possibly also cognitive impairment. However, unlike the bladder dysfunction that follows spinal cord injury, progressive neurological diseases very rarely cause upper tract involvement (Sirls *et al.*, 1994; Koldewijn *et al.*, 1995). This is even the case when long standing multiple sclerosis has resulted in severe disability and spasticity. The reason for this is not known but means that in such diseases, the emphasis of management needs to be on symptomatic relief.

Bladder dysfunction in other non-traumatic spinal cord disease

Cervical myelopathy

Early reviews stated that bladder disturbance was very rare in patients with cervical spondylosis although more recent studies have refuted this (Katz *et al.*, 1988; Hattori *et al.*, 1990a). A variable combination of detrusor hyperreflexia and detrusor sphincter dyssynergia is the commonest urodynamic finding and the majority of patients with these abnormalities have long tract symptoms and signs. However, only recently was a relationship between bladder overactivity and pyramidal signs in patients with cervical cord pathologies demonstrated (Sakakibara *et al.*, 1995a). The neurogenic features of voiding disorder, i.e. hesitancy, poor stream and incomplete emptying, can be easily confused with those that occur due to obstructed outlet (Hattori *et al.*, 1990a).

Syringomyelia, although a benign pathology, can cause progressive spinal cord dysfunction due to expanding fluid within the central spinal canal. Bladder dysfunction usually occurs after other neurological deficits are established (Sakakibara *et al.*, 1996b), although a case where retention was an early symptom has been described (Amoiridis *et al.*, 1996).

An unusual but consistent feature of transverse myelitis is that, although there may be an excellent clinical recovery from a tetraparesis of such severity that at its nadir artificial ventilation is necessary, bladder dysfunction may be the sole residual neurological sequela (Sakakibara *et al.*, 1996a). The explanation for this is not known but it may relate to the emergence of spinal segmental reflexes during the period of 'spinal shock' which then persists as a dominant functional mechanism. This begs the question as to whether bladder function could ever be normalized if treatment were found which enabled regrowth of axons through regions of damage in the spinal cord.

Tropical spastic paraparesis, the progressive myelopathy due to infection by HTLV1 virus, is seen in UK patients of Caribbean origin and in Japan. The myelopathy is slowly progressive over the course of a decade or more with an onset usually before the age of 40 years. Back pain is often prominent (Montgomery *et al.*, 1964). Urge incontinence due to detrusor hyperreflexia occurs as an early feature and may even be a presenting symptom (Cruickshank *et al.*, 1989; Imamura *et al.*, 1991) and detrusor hyperreflexia is the most commonly found urodynamic abnormality (Saito *et al.*, 1991). Recently a characteristic thickening of lamina propria nerves seen on detrusor biopsy specimens from patients with tropical spastic paraparesis has been reported (Dasgupta *et al.*, 1996), the full significance of which remains to be determined.

Once a common cause of bladder dysfunction, neurosyphilis is now rarely seen, but *tabes dorsalis* was classically said to result in an areflexic, hyposensitive bladder due to involvement of the dorsal columns and roots (Brodie *et al.*, 1940). Recent studies of small groups of patients with *tabes* demonstrated a variety of abnormal urodynamic findings (Garber *et al.*, 1990; Hattori *et al.*, 1990b).

Arteriovenous malformations of the spinal cord may be difficult to recognize clinically, but commonly cause bladder disturbance as a prominent early feature. Although the majority of arteriovenous malformations occur in the thoracolumbar region, alterations to cord blood flow and subsequent conus ischaemia mean that the patient may present with what appears to be a conus or cauda equina lesion (Aminoff and Logue, 1974). Symptoms of voiding difficulty are common at an early stage, followed later by urinary retention (Murayama *et al.*, 1989).

A mixture of upper and lower motor neuron signs in the legs together with urinary symptoms is characteristic of a tethered cord. Typically asymmetric wasting of the calves and intrinsic muscles of the feet occurs, but the prominent bladder symptoms and possibly extensor plantar responses suggest a diagnosis of a conus lesion rather than peripheral neuropathy or previous poliomyelitis. Although the majority of cases present in childhood, symptomatic onset in adulthood is probably not as rare as once thought (Pang and Wilberger, 1982). Urodynamic studies show a mixed picture of detrusor hyperreflexia and incomplete bladder emptying and although an improvement in bladder function following a de-tethering procedure has been claimed, the operation is usually carried out to treat pain or prevent progression of neurological deficit (Adamson *et al.*, 1993).

Cauda equina

Damage to the innervation of the bladder in the cauda equina is likely to affect both the anterior and posterior sacral roots containing somatic and parasympathetic fibres. The clinical picture is therefore typically of perineal sensory loss caused by damage to the S2–S4 roots together with loss of voluntary control of both anal and urethral sphincter, as well as sexual responsiveness. The second order parasympathetic innervation running to the detrusor from the spinal cord in the cauda equina terminates in the parasympathetic ganglia which lie in the bladder wall. The detrusor is therefore not denervated but decentralized following a cauda equina injury and the sympathetic innervation of the bladder neck may be preserved. A range of bladder dysfunctions has been described in patients with cauda equina lesions (Nordling *et al.*, 1982; Pavlakis *et al.*, 1983b; Light *et al.*, 1993) including detrusor hyperreflexia (O'Flynn *et al.*, 1992).

The bladder dysfunction that occurs may not be a major complaint, the patient being more preoccupied by the profound genital sensory loss or inability to defaecate normally. Although there are a number of papers reporting the bladder dysfunction that can occur with a cauda equina lesion, there have been few reports on the devastating effect on the quality of life such a lesion can have. However, the levels of compensation awarded in medicolegal cases are reflecting the fact that the loss of control of the pelvic organs and perineal sensation is catastrophic.

Urinary retention has been described following various types of viral sacral myeloradiculitis (Herbaut *et al.*, 1987;

Table 2 *Generalized neuropathies with small fibre involvement*

Diabetes
Amyloidosis—inherited (familial amyloid polyneuropathy) and secondary
Immune mediated neuropathy
Distal autonomic neuropathy (pan/cholinergic dysautonomia)
Inherited neuropathies (inherited congenital sensory neuropathy)

Herbaut *et al.*, 1990; Zeman and Donaghy, 1991) including herpetic infections (Oates and Greenhouse, 1978; Greenstein *et al.*, 1988).

Bladder dysfunction due to disorders of peripheral innervation

The innervation of the detrusor muscle is largely by pelvic parasympathetics which originate from S2–S4 and pass through the pelvic plexus and pelvic nerves. The striated external sphincter muscle is innervated by the same spinal segments via the pudendal nerves. The clinical significance of sympathetic bladder innervation from the thoraco-lumbar outflow is uncertain although the sympathetic innervation of the bladder neck region in men, causing bladder neck closure during ejaculation, is recognized as being important. All three divisions of bladder innervation, parasympathetic, sympathetic and somatic, contain afferent fibres (de Groat, 1990).

Because of its extensive autonomic innervation, bladder dysfunction is most commonly seen in those generalized neuropathies which involve small nerve fibres (Table 2). In countries with advanced medicine, diabetes is the commonest cause of small fibre neuropathy. Small fibre involvement usually occurs as part of a distal, generalized sensory neuropathy but autonomic neuropathy can less commonly occur relatively independently.

'Diabetic cystopathy' (Moller, 1976)

Bladder involvement was once considered an uncommon complication of diabetes but the greater use of techniques for studying bladder function have shown that the condition is often asymptomatic and discovered incidentally (Ioanid *et al.*, 1981). Bladder dysfunction in isolation does not occur and other symptoms and signs of generalized neuropathy may be demonstrated in affected patients. The onset of the disorder is insidious over the course of several years with progressive loss of bladder sensation and impairment of bladder emptying eventually culminating in chronic low pressure urinary retention (Moller, 1976; Ellenberg, 1980). Urodynamic studies demonstrate impaired detrusor contractility, reduction in urinary flow rate and increased post-micturition residual volume and reduced bladder sensation (Buck *et al.*, 1976). It seems likely that there is involvement of both the vesicle sensory afferent fibres causing

reduced awareness of bladder filling and involvement of parasympathetic efferent fibres to the detrusor decreasing the ability of the bladder to contract. The density of acetylcholinesterase positive staining nerves in the bladder wall has been shown to be reduced in diabetics (Van Poppel *et al.*, 1988).

Amyloidosis

Autonomic involvement occurs early in both inherited familial amyloid polyneuropathy and when amyloidosis is secondary to myeloma or benign plasma cell dyscrasia. Typically there are features of somatic sensory involvement such as loss of pain and temperature sensation in the feet when the disease has advanced to produce autonomic involvement. A study of the urogenital complaints of 12 patients with Spanish familial amyloid polyneuropathy type I amyloidosis showed reduced bladder contractility and a reduced flow rate in most of them and two patients had a significant post-micturition residual volume (Villaplana *et al.*, 1997). All were generally very unwell and undergoing liver transplantation and had evidence of severe generalized neuropathy.

Immune mediated

About one-quarter of patients with Guillain–Barré syndrome have bladder symptoms (Zochodne, 1994; Sakakibara *et al.*, 1997). These are usually the patients with more severe neuropathy and the bladder symptoms appear after weakness is established. Both detrusor areflexia and bladder overactivity have been described (Sakakibara *et al.*, 1997).

It is likely that the condition of acute distal autonomic neuropathy is a form of the Guillain–Barré syndrome and there have been a number of reports of distal autonomic neuropathy affecting both the sympathetic and parasympathetic systems. Painful urinary retention usually occurs in both cholinergic and pan dysautonomia (Kirby *et al.*, 1985).

Inherited neuropathies

There is a recessively inherited type II congenital sensory neuropathy in which a sensory disturbance of bladder function has been described with preservation of voluntary micturition (Bardosi *et al.*, 1987).

Injury to pelvic nerves

The peripheral innervation of the pelvic organs can be damaged by extirpative visceral surgery such as resection of rectal carcinoma, radical prostatectomy or radical hysterectomy. The dissection necessary for rectal cancer is likely to damage the parasympathetic innervation to the bladder and genitalia as the pelvic nerves take a medio-lateral course through the pelvis either side of the rectum and the apex of the prostate. The nerves may either be

removed together with the fascia which covers the lower rectum or may be damaged by a traction injury as the rectum is mobilized prior to excision (Mundy, 1982). A prospective study of patients undergoing sphincter sparing surgery for low rectal carcinomas in which each patient acted as their own control, showed that post-operatively there was a significant increase in post-micturition residual urine volume. In 15% there appeared to have been severe damage to the parasympathetic innervation of the detrusor resulting in long-term painless retention, a poor stream, loss of normal bladder sensation during filling and near loss of detrusor contraction pressure (Neal *et al.*, 1981). The incidence of bladder dysfunction following an abdomino-perineal resection for rectal carcinoma is given as considerably higher than 15% if the study is retrospective (Yalla and Andriole, 1984). Urinary incontinence following a radical prostatectomy or a radical hysterectomy, which includes the upper part of the vagina, is probably also due to damage to the parasympathetic innervation of the detrusor and, at least in the case of a radical prostatectomy, direct damage to the innervation of the striated urethral sphincter (Yalla and Andriole, 1984; Leveckis *et al.*, 1995).

Myotonic dystrophy

Although myotonic activity has not been found in the sphincter or pelvic floor of patients with myotonic dystrophy, bladder symptoms may be quite prominent (Sakakibara *et al.*, 1995b) and difficult to treat presumably due to involvement of bladder smooth muscle.

Urinary retention in young women

Urinary retention or symptoms of obstructed voiding in young women in the absence of overt neurological disease have long puzzled urologists and neurologists alike and in the absence of any convincing organic cause the condition was often said to be hysterical. Indeed the largest body of medical literature on the disorder refers to a condition of 'psychogenic urinary retention' (Knox, 1960; Larson *et al.*, 1963; Margolis, 1965; Allen, 1972; Barrett, 1976; Montague and Jones, 1979; Bird, 1980; Bassi *et al.*, 1988; Siroky and Krane, 1991).

Typically the clinical history is of a young woman aged between 20 and 30 years who presents with retention and a bladder capacity in excess of 1 l. The history is often that over the preceding 12 h she has found herself unable to void, and although by the time of presentation she may be highly uncomfortable, she does not have the sensations of extreme urgency that might be expected. There are no other clinical neurological features or laboratory investigations to support a diagnosis of multiple sclerosis, and MRI of the brain, spinal cord and cauda equina are normal. The lack of sacral anaesthesia makes the possibility of a cauda equina lesion improbable.

Fowler and colleagues (Fowler *et al.*, 1988) described a syndrome of urinary retention, the typical clinical features of

which are as outlined above and showed that on concentric needle electrode examination of the striated muscle of the urethral sphincter a striking EMG abnormality could be demonstrated. The abnormal EMG activity is localized to the urethral sphincter and consists of a type of activity which would be expected to cause inappropriate contraction of the muscle. Superficially it sounds like myotonia but detailed EMG analysis shows there are significant differences and the sphincter activity consists of two components, complex repetitive discharges (CRDs) and decelerating bursts (Dyro *et al.*, 1983; Fowler *et al.*, 1985). It is known from other electromyography studies that complex repetitive discharges are due to direct spread of electrical activity from one muscle fibre to another. If single fibre EMG analysis of a CRD is performed a very low 'jitter' can be demonstrated indicating that the potentials forming a CRD are not the result of neuromuscular transmission (Trontelj and Stålberg, 1983; Fowler *et al.*, 1985), but are due to ephaptic spread. CRDs have a characteristic sound over the audio output of the EMG machine and sound either like a motorcycle or helicopter. The other type of activity, the 'decelerating bursts' have been said to produce a sound reminiscent of recordings of whales singing in the ocean (Butler, 1979). Indeed patients with urinary retention in the author's laboratory are referred to as being either 'whale noise' positive or negative. The hypothesis that the activity impaired sphincter relaxation was confirmed recently in a study by Deindl and colleagues (Deindl *et al.*, 1998) who used special hooked-wire recording electrodes to record simultaneous EMG from the urethral sphincter, bladder pressure and urine flow measures.

Why this type of EMG activity should develop particularly in the urethral sphincter is not known. It is a type of activity which the striated urethral sphincter and to some extent the striated anal sphincter muscles are prone to develop, but is rarely encountered in skeletal striated muscle (Jensen and Stien, 1996). It is possible that this relates in some way to the size of the muscle fibres of the sphincters which are known to be of relatively small diameter (Gosling *et al.*, 1981), but the observation by Fowler and colleagues (Fowler *et al.*, 1988) that the women with urinary retention often have polycystic ovaries raises the possibility that the activity is linked in some way to impaired muscle membrane stability allowing direct spread of electrical impulses throughout the muscle, due possibly to a hormonal abnormality. The disorder may possibly be the manifestation of a focal, hormonal dependent channelopathy. This would explain why the condition is seen only in pre-menopausal women.

Whatever the exact cause or nature of the EMG abnormality, it is the commonest finding on concentric needle EMG of the striated muscle of the urethral sphincter in young women with retention. The clinical picture of a woman with this primary sphincter abnormality, however, depends on the reaction of her detrusor muscle to relative outflow obstruction and the same EMG finding has been reported in women with obstructed voiding and detrusor instability (Potenzoni *et al.*, 1983). Others have reported finding this activity in the urethral sphincter

(Butler, 1979; Dibenedetto and Yalla, 1979; Dyro *et al.*, 1983) with a variety of bladder disorders. In a survey of 477 patients referred for neuro-urological evaluation the EMG activity was found in 10% of women and often in association with an increased post-micturition residual volume or a history of recurrent infections (Jensen and Stien, 1996). Webb and colleagues (Webb *et al.*, 1992) found the same activity in eight out of 18 women in urinary retention, but also found EMG abnormalities in the anal sphincter, whereas Jensen and Stien (Jensen and Stien, 1996) found the activity only rarely in the anal sphincter.

The natural history of this disorder was investigated recently by means of a questionnaire sent out to 155 women seen over the last 10 years. The peak age incidence was 25 and retention could have been either of acute or chronic onset, chronic urinary retention being partial and somewhat more common in older women. The EMG abnormality described above is very rarely found in women over the age of 45 years and almost never in post-menopausal women. Many of the women have had an interrupted urinary stream, but been unaware that this is abnormal, so that a voiding history can be quite misleading unless carefully taken. To the patients the difference between being in complete retention and able to pass some urine is tantamount and they may report recovery from former retention if they are able to pass any urine. Being unaware of the extent of their incomplete emptying, they may continue in partial retention with abnormal voiding for months or even years (Swinn *et al.*, 1998). Unfortunately none of the women had themselves discovered an effective treatment and efforts to treat the condition by the hormonal manipulation, injections of botulinum toxin (Fowler *et al.*, 1992) or application of topical nitric oxide cream have been unsuccessful. However, the results of using the recently introduced sacral nerve stimulator are promising (Vapnek and Schmidt, 1991; Elabbady *et al.*, 1994; Everaert *et al.*, 1997) and preliminary results indicate the urinary retention of women with Fowler's syndrome is highly responsive to neuromodulation (Swinn *et al.*, 1998): a woman who has not passed urine per urethram for many months or even years will find that within 24 h of the insertion of a temporary stimulating lead through an S3 foramen and by connection to an external stimulator she is able to void. The mechanism of action of this therapeutic intervention is being actively researched.

Treatment of neurological disorders of micturition

Detrusor hyperreflexia

Anticholinergic medication is currently the most effective treatment for detrusor hyperreflexia. Until the recent introduction of tolterodine, oxybutynin was most commonly used in the UK. This has a relatively selective effect on the parasympathetic innervation of the detrusor muscle but has a frequently complained of side-effect—a dry mouth. It is claimed that tolterodine has the same efficacy but causes less

dry mouth. Where neither oxybutynin nor tolterodine is available, alternatives such as propantheline bromide or imipramine can be tried.

Desmopressin (DDAVP) spray is a nasal spray preparation of a synthetic antidiuretic hormone, first introduced to treat diabetes insipidus. Nowadays it is widely used by children with nocturnal enuresis but in the UK is also licensed for treatment of patients with multiple sclerosis and night-time frequency (Hilton *et al.*, 1983). One or two nasal puffs of DDAVP from a metered-dose spray (Desmospray) administered on retiring reduces urine output for the following 6–8 h, and an oral preparation of DDAVP (Desmotabs) is now available with the same effect. Some patients with multiple sclerosis who were given Desmospray at night chose to use this during the day instead and a placebo controlled trial showed a significant reduction in voiding frequency in the 6 h following treatment and a strong patient preference for the active treatment phase of the study. An increased night-time frequency does not seem to occur in those who use the medication during the day nor is there a significant change in serum sodium levels of the group (Hoover and Fowler, 1998). If hyponatraemia does occur, it usually happens within the first week or so of starting the medication and the chief symptoms are general malaise, headache and visible oedema of the face and ankles. Rapid restitution of the sodium level occurs when the medication is stopped.

Although the prospect of using a nasal spray to control urge incontinence is obviously more appealing to a patient than performing self-catheterization for the same result, prescription of DDAVP should be restricted to patients who understand that the medication is acting on the kidneys rather than the bladder and it can only be used once in 24 h.

Intravesical capsaicin

Intravesical capsaicin has been used to treat intractable detrusor hyperreflexia due to spinal cord disease on the basis that it has a neurotoxic effect on the C fibre afferents which drive volume determined reflex detrusor contractions. Capsaicin has a biphasic action; it is initially an irritant, but if applied in sufficiently high concentration its secondary effect is as a selective neurotoxin acting on unmyelinated afferent C fibres. Patients with detrusor hyperreflexia report an initial deterioration in their bladder symptoms lasting up to 10 days followed by a lessening of urgency and frequency which may last up to 6 months, when the instillation needs to be repeated (Fowler *et al.*, 1994). A controlled study using capsaicin dissolved in alcohol versus the alcohol solution alone has shown capsaicin is the active ingredient (de Seze *et al.*, 1998; Wiart *et al.*, 1998).

A study looking at the effectiveness of intravesical capsaicin in a group of patients with multiple sclerosis found it was most effective in those who were still ambulant (De Ridder *et al.*, 1997). An instillation of lignocaine prior to capsaicin does not appear to lessen the efficacy of the capsaicin and greatly improves the patient's tolerance of the

procedure (Chandiramani *et al.*, 1996). Although intravesical capsaicin has been valuable in demonstrating that the principle of deafferenting the bladder is effective in treating detrusor hyperreflexia, it remains an experimental therapy and in future is likely to be replaced by the ultrapotent capsacinoid, resiniferatoxin. This is an extract from a plant in the genus *Euphorbia* and has been demonstrated to be 1000 times more neurotoxic than capsaicin for the same degree of pungency as capsaicin. Promising preliminary results have been reported using resiniferatoxin to deafferent the bladder of patients with multiple sclerosis (Cruz *et al.*, 1997). Thus, it would seem probable that in the not too distant future detrusor hyperreflexia, at least of spinal origin, will be treated by painless deafferenting bladder instillations.

Incomplete bladder emptying or urinary retention

Incomplete emptying can exacerbate detrusor hyperreflexia, and an overactive bladder constantly stimulated by a residual volume will respond by contracting and producing symptoms of urgency and frequency. Incomplete emptying is particularly likely to occur in patients with spinal cord disease due to a combination of detrusor sphincter dyssynergia occurring during attempts to void and poorly sustained detrusor contractions during the voiding phase.

Since there is no medication which causes effective detrusor contraction at a convenient moment the best option to deal with incomplete emptying or retention has been to use intermittent catheterization. Sterile intermittent catheterization was first introduced in the 1960s (Guttmann and Frankel, 1966), but it was then found that a clean rather than sterile technique was adequate (Lapides *et al.*, 1976). Performed for children with spina bifida and the elderly with disorders of complete bladder emptying (Webb *et al.*, 1990) it has proved highly effective in many patients with multiple sclerosis and various other bladder disorders characterized by incomplete emptying.

Patients are often unaware of the extent to which they empty incompletely, and for this reason measurement of this parameter is the single most important measurement to be made when planning bladder management (Fowler, 1996). The post-void residual volume may be measured either with ultrasound or using in-out catheterization. The advantage of the latter procedure is that it familiarizes the patient with catheterization and so makes teaching the technique of self-catheterization more readily acceptable. A generally accepted figure for significant residual volume is 100 ml.

Intermittent catheterization is best performed by the patient themselves who should be taught by someone experienced in the method. In the UK nurse specialist continence advisors are particularly expert. A main requirement for success with this technique is patient motivation; a degree of physical disability may be overcome provided the patient is sufficiently determined. As a general rule, if patients are able to write

and feed themselves they are likely to be able to perform the technique. Sometimes tremor, impaired visual acuity, spasticity, adductor spasm and rigidity may make it impossible for the patient to do self-catheterization and in such circumstances it may be performed by a partner or care assistant.

Since the principle of this technique is to reduce the post-micturition residue, most patients are advised initially to perform the technique at least twice a day. There is, however, no fixed limit on how often it should be performed, but it should be performed regularly. Doing it only very occasionally provides the opportunity to introduce bacteria without the benefit of regular, complete bladder emptying. Although bacteriuria is noted in 50% of patients doing clean intermittent self-catheterization, the incidence of symptomatic urinary tract infections is fortunately low. Haematuria in the early stages of learning the method is common (Bakke, 1993).

In spinal cord disease, a combination of intermittent self-catheterization together with an oral anticholinergic manages both aspects of bladder malfunction, incomplete emptying and detrusor hyperreflexia. In a patient with a borderline significant residual volume, starting an anticholinergic may have the effect of further impairing bladder emptying. This should be suspected if the anticholinergic has some initial efficacy which then disappears. Also, it is advisable for a patient who has marked hesitancy and difficulty in initiating micturition to wait to start anticholinergic medication until intermittent catheterization has been established, since there is otherwise a risk of developing complete urinary retention. This combined approach works well in all patients with neurogenic bladder dysfunction who have a combination of hyperreflexia and incomplete emptying, provided the patient is not too severely disabled.

Permanent indwelling catheters

Although a combination of anticholinergic medication together with intermittent catheterization is the optimal management for patients with detrusor hyperreflexia and incomplete bladder emptying, there comes a point when the patient is no longer able to perform self-catheterization, or when urge incontinence and frequency are unmanageable. In patients with spinal cord disease this may be reached when the patient is no longer weight-bearing and is chair-bound and at this stage an indwelling catheter becomes necessary.

The most immediate simple solution is an indwelling Foley catheter, but the long-term ill effects of these are well known. One of the major problems may be leakage of urine around the catheter which occurs when strong detrusor contractions produce a rapid urine flow that cannot drain fast enough. A common reaction to this is to insert a wider-calibre catheter, with the effect that the bladder closure mechanism becomes progressively stretched and destroyed. The detrusor contractions may be of sufficient intensity to extrude the 10- or 20-ml balloon from the bladder, further rupturing the bladder neck. The end result is then a totally incompetent

bladder neck and urethra. Bladder stones and recurrent, resistant infections are also more likely in a bladder with an indwelling catheter.

A preferred alternative to an indwelling urethral catheter is a suprapubic catheter which can be inserted under local anaesthetic. However, the procedure should only be undertaken by a trained urologist since there is a danger that bowel overlying the bladder may be punctured, especially in patients with small, contracted bladders. Once *in situ*, the catheter is left on constant drainage because this minimizes the complications which might otherwise result from volume induced hyperreflexic contractions. Closing the urethra is a difficult urological procedure which is not usually attempted, so that continence depends on the suprapubic drain remaining patent. Should the catheter become blocked or kinked, the patient leaks urethrally. Although by no means a perfect system, a suprapubic catheter is a better alternative to an indwelling urethral catheter and is often the method of choice in managing incontinence in patients for whom other means are no longer effective (Barnes *et al.*, 1993).

External device

If urge incontinence is the main problem and the bladder empties completely, some men are able to wear an external device attached around the penis. The simplest and least obtrusive is a self-sealing latex condom sheath, which can be put on each night or kept in place for up to 3 days. More elaborate body-worn appliances are also available, but an expert must fit these. An effective external appliance for women has yet to be devised.

Sacral nerve stimulators

An extradural sacral nerve stimulator can be used to lessen detrusor instability which is proving resistant to anticholinergic medication. The principle by which it is effective is still far from clear but it seems likely that its action is through stimulation of pelvic afferents (Lindstrom *et al.*, 1983). Implanting a stimulator is a two stage procedure. The first stage when the stimulating lead is inserted through an S3 foramen under local anaesthetic is performed as an out-patient. The lead is connected to an external stimulator for 3 days and if the patient's symptoms improve significantly during this time, as judged by measurement of residual volumes and diary recorded voided volumes, they are eligible for a permanent stimulator. This device is implanted in a subcutaneous pocket under general anaesthesia and the stimulating lead tunneled subcutaneously back to the sacrum and the electrode implanted through the foramen. The stimulator is continuously active giving a 15 Hz pulse to the sacral nerves on one side. The implanted stimulators are expensive and the surgical procedure not without complications, but in well selected cases this form of treatment can greatly improve bladder symptoms (Hassouna and Elhilali, 1991; Dijkema *et al.*, 1993).

Nerve root stimulators

In patients who have suffered a complete spinal cord transection but in whom the caudal section of the cord and its roots are intact, the implantation of a nerve root stimulator should be considered. This device was pioneered by Professor Giles Brindley and his collaborators, and more than 2000 have been implanted worldwide (van Kerrebroeck *et al.*, 1993; Brindley, 1994). Stimulating electrodes are applied intrathecally to the lower sacral anterior roots (S2–S4) and the posterior roots are cut. After the implant, adjustments are made to the stimulation parameters so that the patient obtains the maximum benefit from the stimulator, in terms of making the bladder contract for voiding, assisting defaecation or producing a penile erection. This is achieved by stimulating individual roots or combinations of roots. The major benefit from the stimulators is an improvement in urinary continence. This is usually achieved by a combination of increasing bladder capacity, due largely to the posterior rhizotomy that is performed, and improving bladder evacuation. Brindley (Brindley, 1994) has argued that women have greater potential gain from these stimulators than men since incontinence in women is more difficult to manage. Moreover, in men the dorsal rhizotomy that is a necessary part of the procedure will abolish any reflex erections that might otherwise be possible. These stimulators are only suitable for patients with complete spinal cord lesions rather than partial cord lesions or progressive neurological disease.

Urological surgery

Various urological procedures can be carried out to treat incontinence. Although surgical procedures to rectify a bladder disorder causing incontinence in an otherwise fit person are often highly successful, and even following spinal cord injury, a surgical option may be the best solution for long-term bladder management; the same does not apply to those with progressive neurological disease causing incontinence. For example, at a time when the bladder is becoming unmanageable using a combination of intermittent catheterization and oxybutynin, the patient with multiple sclerosis may only just be managing to remain independent and urological surgery is not appropriate. In practice very few patients with progressive neurological disease affecting bladder control opt for surgery, preferring medical management whilst it is effective and a permanent indwelling catheter, a suprapubic catheter in particular, for long-term use.

Conclusion

The neurology of the bladder has received insufficient attention to date but with the changing emphasis of neurology from a speciality concerned primarily with diagnosis to one promoting the treatment and rehabilitation of patients, the recognition that neurogenic bladder disorders cause major difficulties to patients and are often highly amenable to non-

surgical management means this is likely to change. One of the problems which may have stunted interest in this area is the very limited repertoire of symptoms which the neurologically impaired bladder can display. However, having read this review, the reader will not be surprised to learn that it is possible to see an entire out-patient clinic of patients with neurogenic bladder disorders and each have a different underlying neurological disease. All these patients will have in common an anxiety about their bladder dysfunction and eagerness to have it treated.

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