The autonomous bladder: a view of the origin of bladder overactivity and sensory urge

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Incontinence and the generation of excessive sensory urges are common problems that can seriously influence the quality of life of both men and women. The underlying causes have in some instances been associated with uncontrolled bladder activity. However, the mechanisms generating such activity are still poorly understood and pharmacological tools to control it remain relatively ineffective. There are no effective treatments for bladder overactivity possibly because the bladder mechanisms are not understand or targeted. The purpose of this short review is to raise questions and re-visit ideas from some older possibly forgotten and neglected publications, but which may shed new light on this problem.

INTRODUCTION

The bladder of many species including man is rhythmically active during the filling phase. Such activity is generated within the bladder wall and has been described as 'autonomous' activity. Recent work on the nature of autonomous activity has shown that it involves waves of contraction and localized stretches of the bladder wall. The mechanisms generating these complex events are unknown but it has been speculated that they involve a network of pacemaker cells and connecting interstitial cells driven by excitatory and inhibitory neural inputs. The physiological role of autonomous activity is uncertain but the localized stretches may be important in generating periodic sensations in the bladder via rapidly adapting stretch receptors. As the amplitude and frequency of the autonomous activity can be changed, the intensity of the resulting bladder sensations may be modulated by central nervous activity. What is emerging is that there are two distinct mechanisms generating contractile activity in the bladder, autonomous activity and the micturition contraction. From this vantage, a role for autonomous activity in the cause of bladder overactivity can be considered and the hypothesis proposed that 'bladder overactivity is a consequence of inappropriate non-micturition activity', i.e. the 'autonomous bladder' hypothesis. If this overall concept is correct then not only is there a new insight into basic bladder physiology and the origins of the overactive bladder but also the intriguing potential for effectively managing bladder overactivity and sensory urge using specific drugs, while leaving the micturition mechanisms unaffected.

THE BASIC PROBLEM

Incontinence is a common condition affecting millions of people worldwide. In those aged >65 years it has been estimated that nearly 40% of women and 20% of men in the general population have some form of urological complaint which affects their quality of life. Incontinence may be associated with frequent urges to urinate which may or may not be linked to unconscious episodes of raised bladder pressure. It is a major disappointment that basic science and clinical investigations have not yet identified the causes of bladder overactivity or sensory urge, and been able to lead to the development of effective or specific drugs. The answer may be simple; how the bladder works is possibly still not understood. It is therefore time to re-examine the integrated physiology of the bladder to see what might have been missed.

The micturition cycle has two phases; the filling phase in which the bladder accumulates and stores urine, and the evacuation phase or micturition. Much is now known about the physiological and pharmacological mechanisms controlling micturition [1–3]. As the bladder fills, information from receptors in the bladder wall is relayed to the CNS. If it is not desirable to urinate, inhibitory mechanisms are increased to delay micturition. When a critical, but variable, volume of urine has accumulated a neurological 'gate' is opened, activating a complex cascade which co-ordinates sphincter relaxation and bladder contraction.

In comparison, the filling phase has received little attention and less is known about its underlying physiology, partly because many consider that the bladder is not active during filling. This is incorrect; rhythmic contractions of the bladder during filling were first described in human volunteers over 120 years ago and subsequently in several different species (Fig. 1) [4]. This phasic activity is generated within the bladder wall, i.e. the autonomous bladder. For several reasons these basic and potentially important observations have been largely forgotten and ignored. The purpose of this short review is to highlight some recent observations which have led to a re-evaluation of this older work and which may provide new insights into how the bladder works. Importantly, it may also provide a different view of the origins of bladder overactivity and sensory urge, which could be important in developing new approaches to therapy.

THE FILLING PHASE

The introduction of direct measurement of intravesical pressure using cystometry by Mosso and Pellacani in 1882 highlighted two major properties of the bladder during the filling phase. First, the maintenance of a low bladder 'tone' which enabled urine to accumulate with little change in mean transmural pressure; and second, the presence of rhythmic contractions which were not associated with micturition [5].

The ability of the bladder to maintain a low basal tone and how this changed in patients with incontinence and with spinal lesions has been studied in some detail. Currently the generally accepted view is that basal bladder tone, generated by the muscular component of the bladder wall, is controlled by an interplay of excitatory and inhibitory reflexes. The importance of these two mechanisms

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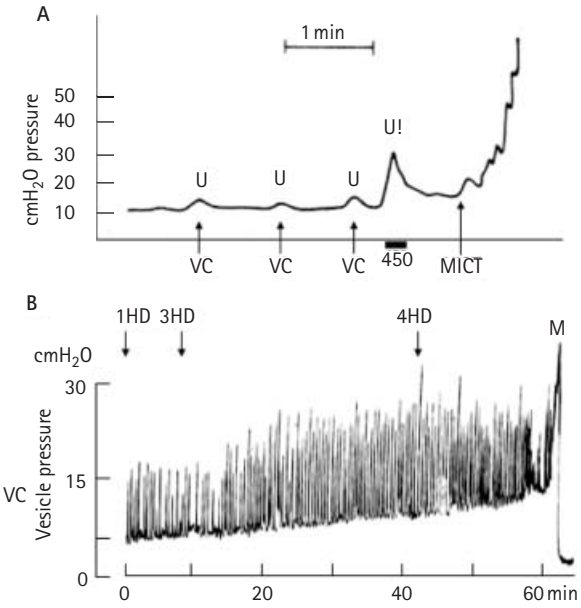
FIG. 1. Non-micturition activity recorded from human and cat bladder. ***A****, a tracing showing changes in intravesical pressure at different volumes in a healthy female volunteer with no evidence of either neurological or urological disease. VC denotes a vesical contraction and U the subject's comment of sensations of urgency. The onset of micturition (MICT) is arrowed and appears as a rapid accumulation of a series of waves. Bladder volume is not stated but may be 450 mL. Time marker 1 min. Taken from [8].* ***B****, non-micturition activity in an intact cat. The bladder was filled artificially at 1, 3 and 4 times the normal rate of urine formation (hour diuresis, HD). Non-micturition activity is seen as phasic activity superimposed on a rising basal tone (tonus). Micturition occurred at M. Redrawn from [4].*



may vary among species. In the filling phase a low bladder 'tone' is maintained by reducing the excitatory micturition reflex (parasympathetic) and promoting inhibitory elements (sympathetic) thus facilitating 'accommodation' [6]. In contrast, relatively little attention was given to the physiological origin and role of spontaneous or rhythmic activity. The reasons for this are unclear but some of the arguments include: (i) rhythmic activity was not prominent in all species [7]; (ii) it was absent in human subjects exposed to stress or pain [8]; and (iii) the magnitude of the activity varied with the anaesthesia [9]. These observations led to the conclusion that rhythmic activity was not of general physiological significance, and interest in it waned.

However, from the earliest studies it became clear that clinical complications associated with frequency and urgency were associated with bladder activity during the filling phase. Therefore, routine clinical cystometry became an important tool to assist in the diagnosis of bladder dysfunction. In the 1970s and 1980s considerable efforts were made to standardise cystometric techniques and establish criteria to quantify bladder function in terms of compliance, capacity and contractility in relation to micturition (see [10] and the publications of the ICS-Standardization Committee 2002). For cystometry to be useful as a routine diagnostic tool it was essential to define the properties of the normal and abnormal bladder. The simplified view that emerged and which is now held by the vast majority of clinicians is that the normal bladder behaves like a passive visco-elastic reservoir in which the stress in the wall is proportional to the intravesical volume. Indeed it has become axiomatic that: '. . . *in normal subjects the bladder should not contract during filling under any circumstances'* and '*a detrusor that is shown to contract, spontaneously or on provocation, during the filling phase while the subject is attempting to inhibit micturition is usually accepted as abnormal and described as "unstable"*' [10].

The value of cystometry cannot be denied; 'unconscious' contractions during filling correlate with clinical symptoms. However, the premise that the normal bladder is an inactive structure during filling is almost certainly wrong. This assumption alone has probably misdirected much of the current thinking about bladder physiology and the origins of bladder pathology. A modification to standard cystometry, ambulatory urodynamics, suggested that significantly many 'normal' individuals with no urological symptoms have bladder activity in the filling phase [11]. This observation has been interpreted in 'clinical' terms as a sub-pathological state in the normal population. This may also be wrong; activity in the filling phase may be normal and subserve key physiological functions. Some of the experimental evidence, based on studies in both man and animals, describing physiological rhythmic activity and the mechanisms which underlie it are reviewed below.

RHYTHMIC ACTIVITY DURING THE FILLING PHASE

In 1882 Mosso and Pellacani [5] described rhythmic activity in the bladders of healthy female volunteers and in dogs. In their animal experiments the rhythmic activity was abolished after spinal transection or rhizotomy, which they interpreted to mean that the rhythmic contractions were driven by central mechanisms. Sherrington, in 1892 [12], noted the presence of rhythmic activity in the monkey, cat and dog. However, he reported that the contractions remained after spinal transection and sacral rhizotomy. The rhythmic activity also persisted after complete peripheral denervation of the bladder and even in the presence of atropine. In a drastic attempt to eliminate these contractions Sherrington removed the bladder and maintained it *in vitro* for several hours; the rhythmic activity persisted. The conclusion he drew was that the activity was an intrinsic property of the bladder wall. This divergence of explanations started a debate which has continued to the present; does rhythmic activity originate within the CNS, a neurogenic origin, or peripherally in the bladder wall, a myogenic origin?

In the years that followed, many studies examined accidental spinal lesions on humans and specific lesions in animals. These investigations showed that rhythmic activity was altered after transecting the spinal cord, by the pelvic (parasympathetic) nerve section

and by sympathetic nerve section (see [13] for an overview). This is perhaps best shown in a study of the cat by Gjone [13]. If the parasympathetic supply to the bladder was interrupted rhythmic activity was reduced or abolished. Subsequent section of the sympathetic nerves re-established rhythmic activity, although reduced in amplitude. In the reverse experiment, first cutting the sympathetic supply caused a marked enhancement of the frequency and amplitude of the rhythmic activity. Interruption of the parasympathetic supply removed this hyperactivity. Thus, a dual parasympathetic and sympathetic influence on rhythmic activity was established. It was specifically noted in a series of experiments by Plum and Colfelt [14] that if great care was taken not to damage the bladder during denervation the rhythmic activity persisted. They coined the term 'the autonomous bladder' to describe the intrinsic rhythmic activity generated within the bladder wall.

The inherent rhythmic activity of the bladder in humans and the effects of neural influences was shown by Plum [8,15] using a group of 'heroic' volunteers. He showed that rhythmic activity was not inhibited by spinal anaesthesia or by parasympathetic ganglion blockade. Plum [8] also noted that if the subjects were nervous or tense the rhythmic contractions were reduced or absent, suggesting the presence of powerful 'psychological' inhibitory influences.

In summary, these studies showed that rhythmic activity was an intrinsic property of the bladder wall, and that the magnitude and frequency of the transient contractions could be influenced by parasympathetic and sympathetic neural inputs as well as influences from higher centres. This then raises further questions: what is the mechanism generating rhythmic activity, how is it regulated and what is its physiological role?

THE ORIGIN AND REGULATION OF AUTONOMOUS BLADDER

Since the work of Sherrington there have been few studies which have investigated the isolated whole bladder and specifically the nature and origins of rhythmic activity (see [16,17]). This was therefore the starting point for a recent study using the isolated whole bladder of the guinea pig. The guinea pig was chosen initially as the structure of the bladder wall with its intramural nerve plexus and ganglia resembles the human bladder [16,17]. As always, the extrapolation of data obtained from one species to another must be cautious because of the variations in anatomy and complex use of micturition, e.g. to mark territory. However, some general principles can be identified and applied.

In the resting isolated bladder of the guinea pig small spontaneous increases in intravesical pressure are a dramatic and obvious feature [16]. A detailed visual examination of the bladder during these pressure microtransients reveals complex propagating waves of contraction and localized stretches of the wall (Fig. 2 [16]). This activity was unaffected by atropine and the neurotoxin tetrodotoxin, which blocks nerve conduction. In the isolated bladder in the total absence of the CNS the mechanisms underlying these basic events must reside within the bladder wall. In keeping with the terminology of Plum this activity in the isolated bladder can be described as autonomous. The movements in the bladder wall can be considerable [16], despite the low amplitude of the intravesical pressure changes. Thus, major physiological evens may be occurring in the bladder wall virtually unrepresented by pressure transients. If this is so then simple cystometry will miss considerable elements of bladder function.

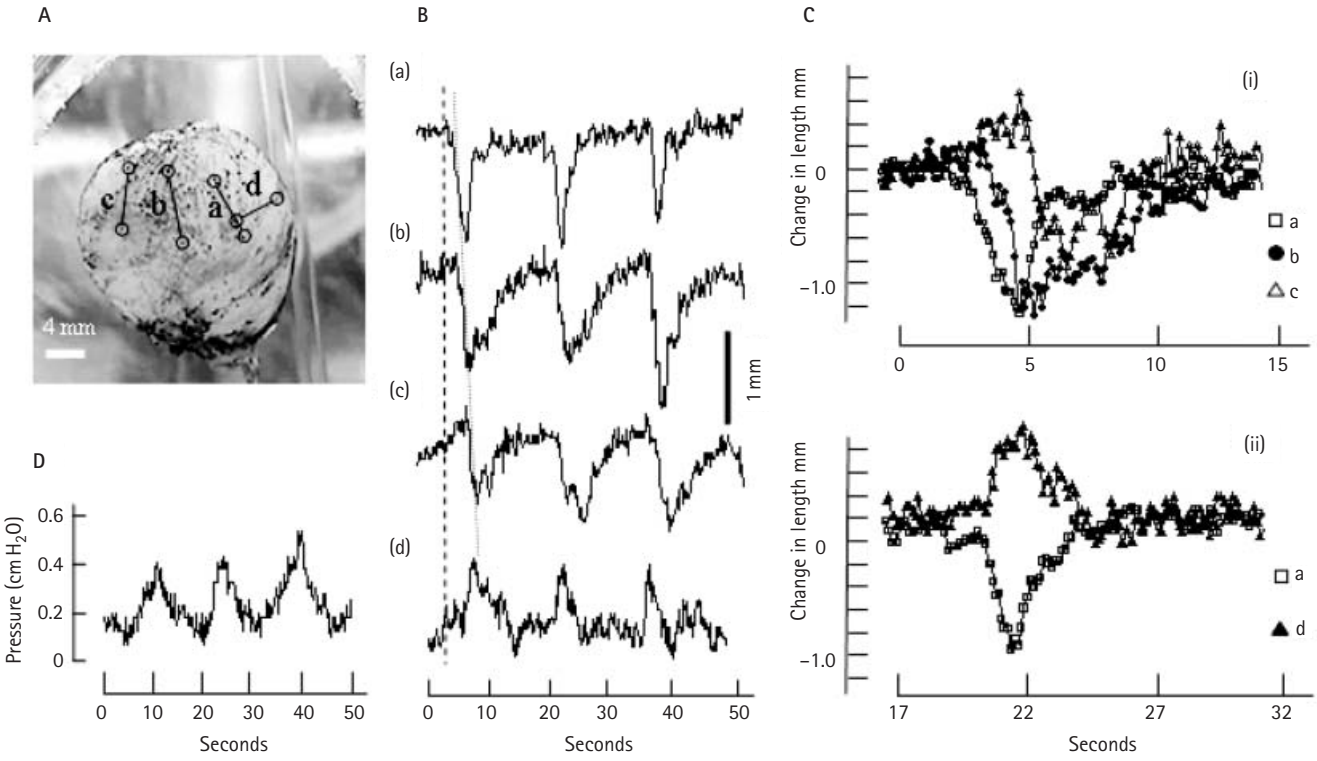
Both the amplitude and frequency of this autonomous activity were increased by muscarinic or nicotinic agonists, resulting in large transient rises in pressure of >20 cmH_2O. These transients were also accompanied by waves of contraction and stretches of the wall [16,17]. The muscarinic induced activity was inhibited by atropine but the nicotinic responses were not. Tetrodotoxin did not affect these augmented transients. Based on these observations, *inter alia* the argument has been proposed that the waves of autonomous activity are not generated by the smooth muscle and propagate by muscle–muscle interactions. The mechanism is therefore not purely 'myogenic', in the sense that it originates in the muscle, and other structures and mechanisms must be involved [16,17]. Also, the observation that autonomous activity augmented by nicotinic stimulation and which cannot be inhibited by atropine or tetrodotoxin implies that the postganglionic parasympathetic nerve fibres involved in micturition are not generating autonomous activity. The underlying mechanism is therefore different from that generating the micturition contraction [17,18].

Two possibilities have been suggested: first, the propagating waves are generated within the intramural nerve plexus involving tetrodotoxin-insensitive neurones [16]. Alternatively, it was proposed that the phasic rises in intravesical pressure are generated by a network of interstitial cells of Cajal, i.e. myofibroblasts [17]. Here there may be a direct analogy with peristaltic activity in the gut. Throughout the gastrointestinal tract interstitial cells are responsible for generating pacemaker activity and propagating activity along the gut wall. The enteric nervous system functions to modulate this activity by both excitatory and inhibitory mechanisms [18]. There is a myofibroblast network within the suburothelial layer. It has been hypothesized that these cells might be important in modulating bladder sensations [19]. In an alternative view it was suggested that they have a motor function and are a focus for neural integration to control motility [17]. What is envisaged is a heterogeneous network of myofibroblasts, consisting of pacemaker cells and conductive cells which augment and co-ordinate autonomous activity.

This 'motor' interstitial cell network would also be the site of integration of inputs from the CNS, other regions of the bladder and the urothelium. The bladder wall has numerous intramural ganglia which form local circuits. The physiological role of such a neural network is unknown [20]. The transmitter agents within these neural elements, when applied exogenously, have little effect on the resting whole bladder but they are highly effective in increasing the frequency of muscarinic and nicotinic augmented autonomous contractions [21]. In addition to excitatory influences there is evidence for inhibition of augmented autonomous activity [22]. Thus, the intrinsic nervous system in the bladder wall has an indirect regulatory role.

It has been known for many years that the bladder is innervated by adrenergic nerves which innervate the detrusor and act via β receptors to induce relaxation and on ganglia which act via α receptors to influence cholinergic transmission [1–3]. Exogenous noradrenaline has been shown to reduce the frequency of the augmented autonomous activity in the guinea pig acting via α_1

*FIG. 2. Microtransient activity recorded from an isolated guinea pig bladder showing a series of spontaneous propagating waves of contraction spreading over the bladder surface. Four regions of interest were identified using pairs of carbon particles randomly placed on the surface (a-d: panel **A**). The displacements of identified pairs of particles are illustrated in panel **B**. The vertical dotted line is shown to accentuate the delay in the initiation of the contraction in successive regions a-c. The oblique dotted line is drawn simply as an additional aid to show that the peak of each episode of shortening occurs later in regions a-c, respectively. **C** shows superimposed records from different areas. (i) shows regions (a) (b) and (c) illustrating the progressive time delay in the initiation of shortening. Note also that a stretch occurs in (c) immediately before the contraction. (ii) superimposes traces from regions (a) and (d). The stretch in (d), commensurate with the shortening in (a) is clearly seen. Panel D shows the accompanying section of a recording of intravesical pressure. Note that despite the relatively large movements of the bladder wall the pressure changes are very small (<1 cmH_2O). A video sequence of this activity can be seen within the electronic version of [16]. Figure reproduced with permission.*



receptors [22]. These responses represent, potentially, an additional action of sympathetic nerves in the bladder. Thus, it would appear that mechanisms generating augmented autonomous activity can be influenced by both excitatory and inhibitory neural influences.

THE PHYSIOLOGICAL IMPORTANCE OF AUTONOMOUS ACTIVITY

The physiological functions of autonomous and non-micturition activity are unknown but it is worth discussing their possible roles. It is accepted that the CNS monitors the functional state of the lower urinary tract more or less continuously throughout the micturition cycle [23]. Receptors in the bladder wall send afferent fibres in both the pelvic and hypogastric nerves which respond during slow filling of the bladder or during the micturition contraction. These receptors are described as 'in series' tension receptors and classified by the conduction velocity of their nerves as Aδ or C fibres [23,24]. As the bladder fills a subpopulation of these afferents, slowly adapting sensory fibres, monitor bladder volume. There are also receptors which are active during the micturition contraction and these are thought to be involved in ensuring that the micturition contraction is complete [23]. A proportion of C fibres do not respond to slow bladder distension at physiological volumes and only fire during overdistension; these probably generate sensations of pain [23].

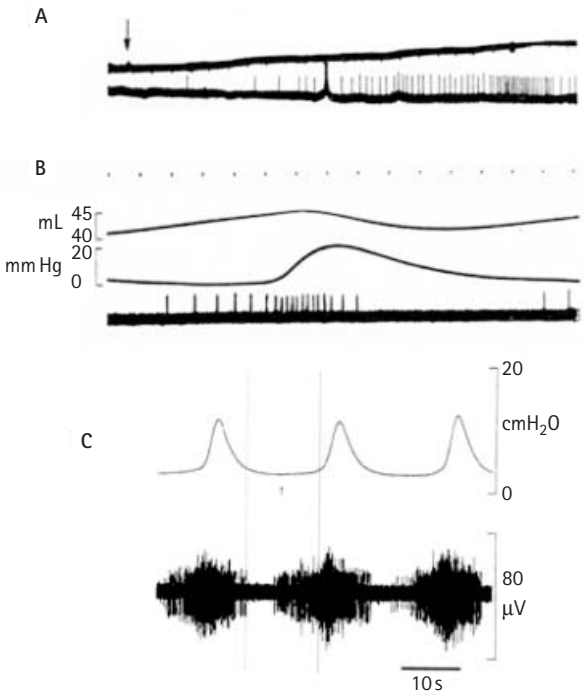
There is also a population of rapidly adapting mechanoreceptors in the bladder wall [24] which respond to rapid changes in bladder volume but are silent during slow filling at physiological rates. This type of receptor has been discounted as contributing to the assessment of bladder volume [23,24] and their physiological role has not been explored. However, it has been known for over 120 years that sensations of urinary urgency are episodic and associated with transient pressure rises in the bladder [5]. It has also been known for over 60 years that the sensory discharge in bladder afferents varies in the frequency which coincides with rhythmic contractions in the bladder [24–26] (Fig. 3C). It was assumed that the rhythmic afferent discharge resulted from synchronous activation of the entire bladder wall. However, the observation of localized contractile activity and stretches may give a new insight into the origins of this phasic neural activity. This may therefore provide a clue to the physiological importance of autonomous activity and non-micturition contractions.

Each non-micturition contraction will involve a localized contraction or a propagating wave of activity which is accompanied by local

rapid stretches of the bladder wall. These stretches will activate rapidly adapting stretch receptors resulting in bursts of activity during each episode. The magnitude of the stretch in each region will depend on the bladder volume and stiffness, which depends on the history of non-micturition contraction. This idea is very similar to that of Coolsaet and van Duyl [27], who detected localized microcontractions in the bladder wall and suggested that they could generate microstretches which would activate nerve endings and contribute to sensations [27]. Thus, information proportional to the bladder wall tension and volume can be relayed to the CNS. The magnitude of the contractions can be increased by muscarinic and nicotinic agonists. In this way it would be possible for the CNS to increase the sensitivity of this sensory input. In addition, increases in the frequency of the phasic activity via purinergic and peptidergic mechanisms and inhibition via adrenergic mechanisms could allow additional regulatory influences and control of the sensitivity of the sensory discharge. In this way it might be possible for the CNS to derive information about bladder volume and to regulate, by augmenting or diminishing non-micturition activity, bladder sensations. The possibility of 'static' receptors monitoring bladder tone and 'dynamic' receptors monitoring non-micturition activity may provide an insight into the different sensations of fullness and urgency perceived by all humans.

In summary, the recent experiments using the isolated whole bladder are leading to the conclusion that bladder activity is controlled by two distinct mechanisms: the 'classical' parasympathetic system which underlies micturition and a second system generating non-micturition activity. The CNS orchestrates both of these systems with the overall coordination and control of the micturition cycle. Micturition contractions involve the overall and synchronous activation of the whole bladder activated by postganglionic cholinergic fibres. Autonomous activity on the other hand involves local activity, propagating waves of contraction and localized stretches of the bladder wall. This activity is intrinsic to the bladder wall but can be modified by parasympathetic motor and sympathetic excitatory and inhibitory mechanisms. These different types of activity may involve different receptors and afferent nerves to relay different information to the CNS.

FIG. 3. Afferent recordings from the pelvic nerve of the cat. ***A****, The afferent discharge from a single unit during the infusion of 50 mL of saline into the bladder (infusion started at the arrow). Upper record, bladder pressure; lower record, nerve activity. The receptor discharge reaches a maximum and then falls silent as the filling reaches completion. Reproduced from [24] with permission.* ***B****, afferent discharge in a single afferent unit during a spontaneous non-micturition contraction. Upper record, bladder volume; middle record, bladder pressure; and lower record, nerve activity. Time markers are 1 s apart. Taken from [24] with permission.* ***C****, changes in intravesical pressure (upper record) and multifibre pelvic afferent discharge. Phasic afferent discharges in time with non-micturition contractions are clear. Reproduced from [26] with permission.*



A FURTHER HYPOTHESIS ABOUT THE ORIGINS OF BLADDER OVERACTIVITY AND SENSORY URGENCY

Based on the current understanding of the micturition reflex and the properties of bladder smooth muscle, two hypotheses have been proposed to account for the uncontrolled bladder activity associated with incontinence. One suggests that unstable contractions arise from inappropriate activation of the micturition reflex: the 'neurogenic theory' [1]. An alternative view proposes that bladder overactivity is generated within the smooth muscle cells of the bladder wall, the 'myogenic theory' [28]. These hypotheses underpin the rationale for most of the pharmacological interventions that have been or are being tried to control bladder function; centrally acting drugs to modulate the micturition reflex, anticholinergic drugs to moderate the micturition contraction and drugs acting to reduce the excitability of the smooth muscle [1–3]. For the vast majority of sufferers, anticholinergic drugs remain the mainstay of pharmacological treatments. However, the efficacy of the anticholinergic drugs is often little better than placebo. It seem remarkable that these different views have not yielded more effective means to manage bladder overactivity. The time is now right to introduce another view of bladder overactivity.

It has been argued here that autonomous activity, non-micturition contractions and phasic sensory discharge, are features of the normal bladder during filling. It is therefore possible that these basic mechanisms might become modified in pathological conditions and abnormal non-micturition activity could underlie bladder overactivity. Inappropriate augmentation of autonomous activity, excessive excitatory inputs or failure of inhibit inputs, could all contribute to uncontrolled excessive bladder activity in the filling phase. Indeed, there is some evidence from the obstructed rat model that rhythmic activity is increased [29]. These ideas may also be

relevant in humans where it has been reported that micromotions are accentuated in women with chronic pelvic pain [30]. This augmented bladder activity would generate excessive afferent discharge and sensations from the bladder. These could be perceived as urges to urinate and would occur spasmodically, coincident with each active phase. The extra 'work' involved in generating excessive non-micturition activity could in the longer term lead to secondary changes in the bladder wall, e.g. smooth muscle hypertrophy and nerve damage. Thus it is possible to introduce a further hypothesis to account for the overactive bladder; 'bladder overactivity is a consequence of inappropriate non-micturition activity', i.e. the autonomous bladder hypothesis. There are similarities between that hypothesis and the neurogenic hypothesis. In both, pathological activity is influenced by the CNS. There are also similarities with the myogenic hypothesis, in that the activity is generated within elements within the bladder wall. However, the autonomous bladder concept develops these ideas further and focuses on specific and new elements which could underlie the causes of bladder overactivity.

There is an important aspect of the autonomous bladder hypothesis which is worth stressing; the basic mechanisms generating and modulating autonomous activity are different from those involved with micturition. Thus there is the exciting possibility that it might be possible to control the initiation and modulation of pathological non-micturition activity without interfering with the micturition reflex. If this proves to be possible then new generations of drugs may become available to control sensations of urgency and incontinence while leaving micturition entirely unaffected.

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