INTRODUCTION
For clinicians with an interest in bladder dysfunction, accurate diagnosis and prognosis remains elusive. The current diagnostic gold standard is fluoroscopic urodynamics despite its acknowledged morbidity and inaccuracies.1-5 Some non-invasive techniques have been evaluated and shown to be useful in the management of bladder dysfunction.6,7 However, if the edict “structure determines function” were true, dysfunction must lend its cause to abnormal structure. Using this edict in attempting to solve the puzzle of bladder dysfunction, the last three decades had witnessed an upsurge in the study of detrusor structure, especially in the field of ultrastructure.

This paper seeks to review our current knowledge on normal, as well as abnormal detrusor ultrastructure seen in non-neurogenic detrusor dysfunction. In particular, a summary of current clinical correlative evidence which may guide future research in this area will be presented.

THE DETRUSOR BIOPSY
Comparison of different biopsy techniques and sites has demonstrated very little variation in ultrastructure of the detrusor throughout its body (which is defined as being above the level of the ureteric orifices).8-10 This includes transabdominal ultrasound-guided needle biopsy and autopsy specimens.8,9 However, the standard biopsy is taken transurethrally from the body detrusor, approximately 2 cm supero-lateral to the ureteric orifice.10-13 No study has been able to detect a difference between detrusors of different ages or sexes.10,11,13-16

NORMAL DETRUSOR ULTRASTRUCTURE
On light microscopy, the detrusor musculature consists of spindle shaped smooth muscle cells with a single nucleus.17 Under electron microscopy, numerous mitochondria and occasional endoplasmic reticulum and Golgi apparatus may be seen.18 Clusters of ribosomes and dense bodies may be seen throughout the sarcoplasm. The cell membrane (sarcolemma) consists of alternating dense and thin bands. Rows of caveolae (flask-shaped surface vesicles) may appear at the thin zones (Fig 1, 2).

The gross architecture of the detrusor is an interwoven non-layered network of muscle bundles.17,19 This arrangement can be appreciated by light microscopy or by electron microscopy at low magnifications (x 1000-3000).

The muscle “fascicle” is the smallest recognisable compact unit consisting of four to twelve cells closely aligned (less than 0.2um spaces), unidirectional and separated by a thin microsepta of collagen fibrils and occasional elastin.4 An aggregate of these fascicles is known as a muscle “bundle” and is surrounded by a thick interstitial macrosepta of collagen, elastin and occasional fibroblasts (Fig. 2, 3). Only a proportion of myocytes are directly stimulated by neuroeffector junctions, the majority receiving the stimulus to contract via mechanical coupling or electrical coupling via intercellular junctions.18 Therefore axon bundles are sparse in the interstitium and may be difficult to identify on electron microscopy (Fig. 4).

Fig. 1 – Normal detrusor (x 7450, 931/10). The dense band pattern of sarcolemmal alternating thick (bright) and thin (barb2right) cell membrane is seen. Note the flask-shaped surface vesicles (“caveolae”) at the thin zones. The interstitium is mostly comprised of collagen (c) with its pine-needle appearance. Elastin (e) is seen as small aggregates of dense amorphous material. Several normal ICJs are seen (*).
Intercellular junctions are an important ultrastructural feature of the detrusor. The most common junction is the intermediate cell junction (ICJ or “zonulae adherents”). This consists of two closely apposed (25-70nm wide gap) sarcolemma lying parallel to each other for a length of up to 10 µm with paired symmetrical dense plaques. Other junctions are less common in the normal detrusor and are known as “gap junctions” owing to their tight apposition. These include “protrusion junctions” which are slender finger-like projections between cells with tip-to-tip contact, and “ultraclose abutments”, which are a tight apposition of parallel surfaces in a shallow bump-impression configuration (Fig. 5).

ABNORMAL DETRUSOR ULTRASTRUCTURAL FEATURES

True pathological ultrastructural features may be considered as changes to the overall architecture, to the interstitium, the myocyte or to the nature of the cell junctions. In various combinations, these features have been correlated with urodynamically diagnosed voiding disorders.

Abnormal Detrusor Architecture

Detrusor fascicle arrangement becomes pathologically distorted in diseased bladders. This is largely a qualitative description of the uniformity and close apposition of adjacent myocytes within fascicles. Various gradings have been proposed, with the clearest (albeit qualitative) from Hailemarium and Elbadawi as: 1) “Compact” – a fascicle-bundle unit with only mild uneven myocyte separation; 2) “Intermediate” – a mixture of uniform units and occasional intermediate or loose fascicles; and 3) “Loose” – mostly moderate to marked myocyte separation or indistinct arrangement with rarely seen uniform units (Fig. 6-8).

These changes are seen most markedly in the hypocontractile detrusor and in bladder outlet obstruction. This abnormal architecture is closely associated with the abnormal interstitial content. The amount of collagen and elastin increase with increasingly distorted fascicle arrangements. In normal amounts collagen reinforces mechanical cell coupling, and has a key role in the eventual summated unitary detrusor contraction, leading to the complete expulsion of urine. However, excessive intercellular collagen is thought to dissipate forces achieved by contracting myocytes. This may lead to the clinical correlate of residual urine. Also, collagen being one of the stiffest biomaterials known, could increase rigidity and reduce compliance. Elastin, the most stretchable biomaterial known, would promote distensibility and may allow the bladder capacity to increase dramatically in chronic retention with overtension (Fig 6-8).
Abnormal Cellular Profiles

Myocytes may hypertrophy, typically correlating with bladder outlet obstruction (Fig. 6). Cell shape, density and content must also be considered. Abnormally shaped myocytes may be branched (like fork-prongs), braided and intertwined (“hugging” each other) or bizarre shapes such as cannelloni. These abnormal shapes (versus the normally spindle-shaped myocyte) may also cause contractile forces to dissipate and wasted upon itself. Hypertrophic contorted myocytes are usually seen in association with loose fascicles, and therefore do not guarantee a stronger detrusor contraction as forces are attenuated, especially by the increased interfascicle distance by increased collagen deposition.

The myocyte shape and content can be indicative of detrusor degeneration, with the clinical correlate being hypocontractility. This may range from a cell containing vacuoles and debris, to a fragmented cell with sequestration or even a shrivelled dense cell without internal structure (Fig. 7). These disrupted cells may be the cause or effect of bladder dysfunction. They would presumably impair contractility or may be the result of a poorly contractile bladder with overdistension and patchy hypoxia in stretched muscle (Fig. 8).

Abnormal Intercellular Junctions

The ultrastructural feature requiring the highest magnification to accurately assess is the intercellular junctions (ICJ). Initial researchers noted increased gap junctions in patients with urodynamics detrusor overactivity and they were considered an abnormal feature. However, gap junctions are seen in urodynamically normal detrusor. What has clearly been demonstrated is that their ratio compared to normal ICJs increases with detrusor overactivity. These detrusors demonstrate a syncytium pattern of indiscernible gaps between cell processes linking up to ten myocytes or more. This ultimately changes the nature of the summated detrusor contraction. Instead of predominant mechanical cell coupling via the ICJs during detrusor contraction, a low resistance pathway is created by the presence of these gap junctions, thus mediating rapid electrical coupling. This results in the unstable contractions seen on urodynamic studies of subjects with an overactive detrusor.

HOW DO THESE ULTRASTRUCTURAL FEATURES CORRELATE WITH CLINICAL FINDINGS?

Many of the original ultrastructural descriptions were based on very small numbers of patients, with variable urodynamic definitions. Subsequent studies have confirmed and refined these features. Ultrastructural categories were created and those which persist today are defined as the following: 1) the myohypertrophy pattern of bladder outlet obstruction (with hypertrophied, contorted myocytes and loose fascicles), 2) the dysjunction pattern of detrusor overactivity (with presence of gap junctions and intermediate fascicles); and 3) the degenerative pattern of detrusor failure (vacuolated lytic cells with intra- and extra-cellular debris). As a subcategory, hyperelastosis (excessive elastin deposition) seems to correlate with chronic urinary retention, although not all studies agree.

Clinical studies show some discrepancies in their findings. The greatest variables between studies are the definitions used for voiding diagnoses (including definitions of controls), use of urodynamics, the technique of ultrastructural analysis, and the specimen processing technique.

Starting with the myohypertrophy pattern, Elbadawi originally studied seven patients with bladder outlet obstruction determined by fluoroscopically guided micturitional urethral pressure profilometry, in some patients corroborated by pressure-flow analysis. In a further validation study five patients with clinically moderate obstruction had more pronounced loose fascicles than 3 patients with mild obstruction (according to Schafer’s nomogram). Briefly assessed 12 patients awaiting prostatectomy for urodynamically-proven bladder outlet obstruction. Only eight patients demonstrated the myohypertrophy pattern and there was no apparent association between the urodynamic variables and the presence of myohypertrophy. Three of the 17 controls showed some limited myohypertrophic features, although these were not extensive enough to fulfill the criteria used. In Holm’s study of 25 patients with bladder outlet obstruction, the myohypertrophy pattern was not observed in any of the biopsies when compared to six controls. This raises many questions, however the methodological error in this paper was clearly different to that of the positive relative studies. These differences included specimen...
processing technique and inclusion of patients with “equivocal” obstruction.

Elbadawi’s original description of the dysjunction pattern as the presence of abnormal gap junctions was based on 15 patients with detrusor overactivity. In a later validation study by the same researchers it was found that patients with normal urodynamics also displayed gap junctions. More recently, Tse’s quantitative analysis showed a significant stepwise increase in the ratio of gap junctions to ICJs in four groups respectively: controls, idiopathic sensory urgency, bladder outlet obstruction with overactivity, and idiopathic detrusor overactivity. However, Carey’s qualitative ultrastructural study of 13 women with idiopathic overactivity did not detect any gap junctions. In this study there was considerable interobserver variability between two reporters, with only two patients for which there was tabulated agreement. This brings into question the qualitative nature of ultrastructural reporting on the whole and the need to objectify all aspects as much as possible.

Degeneration was originally described in ten elderly patients with hypocontractile bladders, defined as post-void residuals (PVR) of greater than 250ml. The definition of normal PVR is subject to controversy, although a consistently “significantly” elevated PVR is considered indicative of relative detrusor failure. Collins studied 19 patients with PVRs greater than 250ml. Eleven underwent prostatectomy. The degenerative pattern was seen in conjunction with myohypertrophy in all patients and the severity of degeneration correlated with post-prostatectomy voiding. Hindley found the degeneration pattern in all 20 patients with PVRs greater than 300ml. A study of 12 patients awaiting prostatectomy demonstrated the full degenerative pattern in the six patients with the highest PVRs (all greater than 150ml). In a study of 14 patients with PVRs greater than 500ml compared to controls (with PVRs up to 160ml), Holm found degeneration in all patients and five of six controls.

Four of his six controls suffered from lower urinary tract symptoms and two had previous bladder cancer. Accepting that some degenerative features were often noted in controls, Brierly conducted a quantitative study by counting the “disrupted cell ratio” as the number of disrupted cells per 500 cells. A significant difference was demonstrated between controls and patients with detrusor hypocontractility.

Finally, in a study aimed to assess all of Elbadawi’s originally described ultrastructural patterns, Mastropietro was unable to significantly correlate any of the patterns with urodynamic diagnosis of voiding dysfunction. He concluded that some degenerative features could then be established by multivariate analysis.

CONCLUSION
Evidence has been accumulating of a definite relationship between structure and function of the detrusor for many years. Starting with the breakthrough work of Elbadawi, distinct ultrastructural features were for the first time correlated with functional urodynamc parameters. This work has been subsequently expanded upon by many authors, and the methodology and definitions refined. Despite all this work, a definite clinical role for ultrastructural detrusor analysis has yet to be established.

Inconsistent findings of degeneration, myohypertrophy, hyperelastosis and dysjunction patterns in clinical validation studies suggest a need to reassess the significance of individual features rather than rely on the traditional patterns originally outlined by Elbadawi. These individual features could then be analysed by multivariate analysis with urodynamic and outcome parameters. One potential future research area is whether the ultrastructure reverts towards normal after treatment of the bladder dysfunction. E.g., after successful treatment of overactivity or bladder outlet obstruction.

Current work is underway by the authors in looking at gap-junctional protein expression in urodynamically abnormal detrusors in the quest for further refining a structural-functional correlate in common bladder dysfunctions. We also hope this paper may assist and encourage future research in identifying a diagnostic and prognostic role for ultrastructural study of the detrusor.

REFERENCES
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**Pelvic Floor Digest**

Significance of tension in tension-free mid-urethral sling procedures: a preliminary study. Paick JS, Oh JK, Shin JW et al. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:153-8. The results of the release and tape-shortening techniques in polypropylene submucosal mid-urethral slings are reported, tension playing a substantial role in restoring continence or experiencing urinary retention or other voiding difficulties.

13 years of experience with artificial urinary sphincter implantation at Baylor College of Medicine. Lai HH, Hsu EI, Teh BS et al. J Urol 2007;177:1021-5. Between 1992 and 2005, 270 patients underwent artificial urinary sphincter implantation (single surgeon). Of the 218 patients followed-up 176 underwent undergone prostatectomy with or without pelvic radiation, 11 had neurogenic bladder and 31 underwent secondary artificial urinary sphincter implantation. Complication rates were infection in 5.5% of cases, erosion in 6.0%, urethral atrophy in 9.6%, mechanical failure in 6.0% and surgical removal or revision in 27.1%. At 5 years 75% of patients had avoided revision or removal.


Complications of sling surgery among female medicare beneficiaries. Anger JT, Litwin MS, Wang Q et al. Obstet Gynecol 2007;109:707-14. Complication rates within 1 year after sling surgery among Medicare beneficiaries were found to be higher than those reported in the clinical literature. The high rates of postoperative urinary tract infections, prolapse, and outlet obstruction suggest the need for quality improvement measures in the management of women with incontinence and pelvic prolapse.

Anatomic comparison of two transobturator tape procedures. Zahn CM, Siddique S, Hernandez S, Lockrow EG. Obstet Gynecol 2007;109:701-6. To compare inside-in (Monarc) and inside-out (TVT-O) methods for transobturator tape placement regarding proximity of the tape to the obturator canal and ischiopubic rami, 7 cadavers were dissected to the level of the obturator membrane measuring the distance from the closest aspect of the obturator canal and ischiopubic rami to each tape. The inside-out technique results in the mesh being placed farther from the obturator canal and closer to the ischiopubic rami, theoretically reducing the risk of neurovascular injury.

Comparison of cystographic findings of intrinsic sphincteric deficiency with urethral hypermobility causing urinary incontinence. Park SW, Sung DJ, Choi EJ et al. Urol Int 2007;78:116-20. Intrinsic sphincter deficiency should be considered in female patients with symptoms of urinary incontinence where there are changes in posterior urethrovaginal angle <20 degrees on a lateral cystogram between a stress state and resting state in addition to the beaking sign of the vesical neck during a resting state.

Sacral nerve stimulation for neurogenic faecal incontinence. Holzer B, Rosen HR, Novi G et al. Br J Surg 2007 Apr; 4. Epabd. Thirty patients with faecal incontinence of neurogenic etiology were included in a trial of SNS and 29 had a permanent implant. Evaluation consisted of a continence diary, anal manometry, saline retention testing and quality of life assessment. After a median follow-up of 35 (range 3-71) months, 28 patients showed a marked improvement or complete recovery of continence. Saline retention time increased from a median of 2 (0-5) to 7 (2-15) min. Maximum resting and squeeze anal canal pressures, and quality of life on all scales, increased at 12 and 24 months after operation.

Internal anal sphincter defect influences continence outcome following obstetric anal sphincter injury. Mahony R, Behan M, Daly L et al. Am J Obstet Gynecol 2007;196:217.e1-5. To define the correlation between the extent of anal sphincter injury as seen by endoanal ultrasound and symptoms of postpartum fecal incontinence, 500 women were studied at 3 months following primary repair of a first recognized obstetric anal sphincter injury during vaginal delivery. US evidence of internal anal sphincter injury is predictive of severe incontinence (score greater than 9/20).

National audit of continence care for older people: management of faecal incontinence. Potter J, Peet P, Mian S et al. Age Ageing 2007 Mar 13; 13. Epabd. Fecal incontinence in older people is associated with considerable morbidity but is amenable to successful management. Basic assessment and care for truly integrated continence care for the professionals directly looking after older persons however is often lacking and there is an urgent need to re-establish the fundamentals of continence care into the daily practice of medical and nursing staff.

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