Quick note on tissue engineering-based surgical measures to treat patients with neurogenic bladder-due detrusor/sphincter dyssynergia

Ann. Ital. Chir., 2015 86: 252-257
pii: S0003469X15023623
www.annitalchir.com

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L.D. of Surgical Semeiotics

Quick note on tissue engineering-based surgical measures to treat patients with neurogenic bladder-due detrusor/sphincter dyssynergia

To treat the neurogenic bladder-due detrusor/urethral rhabdosphincter dyssynergia, early combined clean intermittent catheterization/pharmacotherapy (anticholinergic-, β3-adrenoceptor agonist drugs) management may be at times crowned with success of preserving an adequate bladder compliance and renal safe conditions. The persistence, instead, of elevated bladder filling pressure levels with high voiding pressure/uroflow values, together with aberrant urethral rhabdosphincter electromyographic findings, make necessary the resort to surgery strategies, among which – a part from rhabdosphincterotomy or alternatively intrasphincteric botulinum A toxin injection or urethral stent insertion – the bladder augmentation cystoplasty, with either reconfigurated bowel- or gastric segment, is today the most efficacious surgical measure to increase the bladder urinary storage meanwhile lowering bladder filling pressure. Given the enterocistoplasty-dependent both potential systemic metabolic imbalances – such as hyperchloremic acidosis/hypokaliemia, hyperoxaluria, bone demineralization, cholegenic diarrhoea/steatorrhoea, vit B12 deficiency – together with bowel prosthetic mucus overproduction-due recurrent stone formation, and, sometimes, malignant complications particularly at the intestinal-urinary tract suture line, tissue engineering techniques have been taken into consideration, more than twenty years ago, as alternative measure for bladder augmentation cystoplasty, until to reach successful clinical validation just in patients suffering from either congenital dysraphism- or acquired spinal cord injury-dependent neurogenic bladder. Nevertheless, also the tissue engineering-made augmentation cistoplasty, as well as that bowel-based one, unfortunately remains influenced by spinal cord neuropathy-due dysfunctional effects, hence the tissue engineering research could be today directed to suitably overcome such disadvantageous conditions.

KEY WORDS: Augmentation cystoplasty, Pediatric surgery, Tissue engineering scaffolds, Urology

Introduction

Among the various manifestations of the neurogenic bladder, the impairment of detrusor/external urethral sphincter (rhabdosphincter) synergic coordination – as, indeed, the sphincteric contraction simultaneously to micturition, just so-called *detrusor-sphincter dyssynergia* (DSD) – due to neurologic lesions at different levels between the pontine micturition centre and that sacral spinal cord one (Table I), acts as the most considerable pathophysiological disorder leading to bladder outlet functional obstruction with a dangerous increase in both filling and voiding bladder pressure, up to give rise to renal damage [1-3].

In effect, bladder filling pressure high levels, compared with the normal ones less than 10-15 cm H_2O – particularly with elevated "leak point" pressure more than 40 cm H_2O – and, in addition, the increase in bladder voiding pressure (whose normal values are 50-80 cm

Pervenuto in Redazione Dicembre 2014. Accettato per la pubblicazione Marzo 2015
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H_2O for men and 40-60 cm H_2O for women), lead to the vesicoureteral reflux onset and/or the urine pyeloureteral drainage lowering with decrease in glomerular filtration rate until to renal failure, what's more when such conditions are worsened by recurrent urinary infection-due pyelonephritis [1].

Preventive and therapeutic medical measures

The early postnatal assessment of DSD (Table I) makes feasible the timely beginning of *clean intermittent catheterization* (CIC) treatment together with administration of either *anticholinergics* (muscarinic-3 receptor blockers, such as oxybutynin, tolterodine, solifenacin, trospium as well as propiverine, that's endowed with calcium-antagonist properties too) or β3-*adrenoceptor agonists*, such as mirabegron, or even, for the neurogenic bladder refractory to drug therapy, the into detrusor *botulinum A toxin* injection [1,4,5].

Such, early adopted in infancy, combined measures are at times crowned with significant benefits among which preservation of a suitable bladder compliance, prevention or ready suppression of vesicoureteral refluxes, so it proving to be paramount to foresee a long term kidney safe conditions, in comparison with the unreliability of neurogenic bladder management restricted to the only"wait and see" watchful observation [1,4,6].

Intriguingly, it has been shown, by an experimental research in spinal cord injured rats, that the herpes simplex virus vector-based delivery of GAD (glutamic acid decarboxylase, changing the glutamate to γ-aminobutyric acid, GABA) gene to bladder afferent nervous pathway, can lead – by inhibitory effects on excitatory brain stem-spinal neurotransmitter glutamate – to lower the urethral rhabdosphincter resistance during bladder mictional contraction, what making foreseeable a possible innovative approach to treat the spinal damage-due DSD [7]. Moreover, the histone deacetylase epigenetic inhibitors trichostatin A and valproic acid prove to be effective, *in vitro*, to decrease the collagen overproduction from neurogenic bladder-derived smooth muscle cell culture, that's why such drugs could be used to prevent the bladder fibrosis in patient suffering from this disease [8].

Basic surgical management

Though the early combined CIC-pharmacotherapy may be long-term useful to prevent, in the DSD disease, the decrease in bladder compliance with following renal function damage, otherwhise the persistence of high bladder filling pressure values with worsening disease, make necessary the resort to surgical measures [3].

A part from either the insertion of a urethral sphincteric stent or intrasphincteric *botulinum A toxin* injection or even resection of urethral rhabdosphincter, together with a possible anti-vesicoureteral reflux operation (ureterocystoplasty), the most common surgical measure consists in the bladder augmentation cystoplasty using either a reconfigurated intestinal- or gastric segment to increase bladder compliance with following decrease in filling/emptying bladder pressure [3,9-12]. Quite out of the current use is, instead, the detrusor multiple myotomy-based bladder autoaugmentation as no fulfilling any good expectation.

TABLE I - *Neurogenic bladder-related DSD: essentials on aetiology and diagnostic assessment*

AETIOLOGY

Congenital diseases

– either open or occult dysraphism/myelodyplasia, due to folic acid deficiency in childbearing age women and related to folate metabolism-involved genes. Particularly, mutations of VANGL 1 gene seem to be a risk factor for neural tube defects (2).
– sacral agenesis.

Acquired diseases

– spinal cord injures from sporting/motor vehicle/at work accidents or occurring iatrogenically after aortic-vascular or spine surgery; transverse myelitis, spinal tumors, multiple sclerosis.

DIAGNOSTIC ASSESSMENT

– serum creatinine;
– post-void residual volume;
– renal and bladder ultrasonography;
– urodynamics: bladder compliance (bladder volume/detrusor pressure ratio); bladder filling-voiding pressures; bladder pressure-uroflow profile; combined urodynamic tests-fuoroscopic videoimaging;
– rhabdosphincter electromyography(particularly, electromyographic-uroflow profile study);
– motor unit potentials;
– X-ray imaging: intravenous pyelography and, particularly, voiding cystourethrography (VCUG);
– three-dimensional bladder-kidney holographic imaging (US, CT, RM);
– radionuclide imaging: static renal scan, functional diuresis renogram, radionuclide VCUG.

Unlike that colonic/sigmoid one, the most commonly bowel segment used for the augmentation cystoplasty is the ileum, whose detubularization on the antimesenteric border with fashioned into either "U" or "W" shape, allows to achieve a low pressure compliant reservoir. Unfortunately, several systemic metabolic imbalances resulting from either the exposure of absorptive intestinal mucosa to urine – hyperchloremic acidosis/hypokaliemia, bone demineralization because of bone calcium carbonate-phosphate dissolution due to excess of serum hydrogen ions – or the removal of ileal segment – chologenic diarrhoea/steatorrhoea, hyperoxaluria, vit. B12 deficiency, hypocalcemia/hypomagnesiemia – lead to discredit, together with bowel prosthetic reactive mucus overproduction-dependent recurrent stone formation besides the possible onset of malignant pathomorphosic entero-prosthetic complications, the resort to bowel for the bladder augmentation [13,14]. In this regard, the gastric augmentation cystoplasty shows, instead, a lower onset of metabolic-electrolyte imbalance – a part from sometimes the metabolic alcalosis – and has the advantage of less mucus production [4,11,12].

Just to avoid such deleterious events and otherwise given that the use of intestinal segments in bladder reconstructive surgery results to be impracticable in some conditions – such as short gut syndrome, chronic inflammatory bowel disease, previous abdominal-pelvic irradiation – research, at the 90s of the last century, has been turned to apply the tissue engineering technology to bladder augmentation cystoplasty [15-17].

Outlines on tissue engineering technologies to build wall bladder tissue

Such technologies provide intriguing opportunities to create *de novo* a tissue endowed with both urothelium barrier/sensory transducer- and bladder smooth muscle cell contractility properties. Besides ECM (extra-cellular matrix) component materials (collagen, laminin, elastin, hyaluronic acid, alginate, chitosan) and acellular tissue matrices (ABS, acellular bladder submucosa; SIS, small intestinal submucosa), several biodegradable *synyhetic materials* (from, at first, polylactic acid, PLA, or polyglycolic acid, PGA and PLA-co-PGA acid, PLGA, to, more recently, electrospinning-produced fibrous polyurethane/terephthalate) have been used as a tailored scaffold for either "unseeded" (cell free) or "seeded" (with autologous either differentiated- or stem cells) tissue engineering modalities. Unfortunately, unseeded tissue engineered bladder constructs show, in the course of time, a wall fibrosis-due shrinkage with inadequate compliance [18-22].

The use of different types of stem cells – from *natural stem cells* including embryonic-, fetal-, and adult stem cells to *laboratory procedure-generated stem cells* as by either somatic cell nuclear transfer-mediated therapeutic cloning or adult somatic cell genetic reprogramming – avails of their peculiar active properties as self-renewal and specific cell lineage differentiation under adequate microenvironmental conditions (growth factors, cytokines, etc), so to be an intriguing source of mature cells for various tissue engineering applications among which, specifically, the bladder augmentation cystoplasty [23-26].

Out of thorougly synthesis-obtained biomaterials, the Bombix mori (or even spider) *silk fibroin,* at times tested in animal models to either coat the surface of polyurethane scaffolds or create a bilayer silk fibroin/SIS constructs, has been also used as template for bladder tissue engineering, it showing good both structural and mechanic properties, such as biodegradability and plasticity [27,28].

Clinical validation of *de novo* tissue engineering-based bladder wall fabrication – by means of autologous mature urothelial/smooth muscle cells seeded onto a composite PGA-collagen made 3D scaffold – has been, at first, successfully achieved, thanks to Atala and his group, by implanting such construct, with omental drap, in patients needing augmentation cystoplasty as suffering from myelomeningocele-induced poorly compliant/high pressure neurogenic bladder [29,30]. More recently, a tissue engineered augmentation cystoplasty, for treatment of neurogenic bladder, has been successfully obtained by using SIS as a scaffold to rebuild a functional bladder tissue [31]. Significant research projects are more and more intended to develop tissue engineered bladder constructs that can allow, besides a suitable compliance, also a native-like contractile prosthetic tissue-mediated efficacious micturition . Keeping to recent literature reports, it seems, indeed, that BAM (bladder acellular matrix) might be used to obtain a cell-seeded graft with possible hope of fabricating "off the shelf" replacement materials for augmentation cystoplasty [31,32]. Nevertheless, for patients with CIC-drug therapy refractory neurogenic bladder-dependent DSD, any augmentation cystoplasty measure – so, even that tissue engineered-based – remains conditioned, as it's well-known [33], by spinal cord neuropathy dysfunctional effects. Hence it would be suitable, for these subjects, to prepare a tissue engineered neobladder-urethral rhabdospincter complex construct – "idea" more easely conceivable rather than feasible and otherwise questionable as far as the below-pointed out clinical implications – that proves to be free from spinal cord neuropathic effects. Such construct might be made up of neobladder wall provided with embedded tension biomicro-electro-sensors (correlatively to intra-neobladder pressure) with micro-loop antenna to send, beyond a properly-subjectively adjustable wall tension value threshold, modulated wireless e-m signals toward a neo-rhabdosphincterial receiver/converter micro-electro-device to promote, in turn, by a suitable rhabdosphincter-tone-contraction inhibitory e-m field generation, its relaxation simultaneously with the neobladder contraction . What should be quite reversible following the micturition-due intra-neobladder pressure drop below the arranged levels [34].

As it has been above mentioned, such tissue engineered complex structure may be, in my opinion, fairly questionable given its functional features like "autonomous neurogenic bladder", that pathologically results from loss of both sensory and motor innervation [35,36]. Nonetheless, by also endowing the neobladder construct component with a intramural micro-electro device open to voluntary activation through wireless e-m signals transmitted from a special outside personal electrostimulator, it could make possible a voluntary micturition.
Intriguing advances in the field of material science research to build different scaffolds – from various "smart" synthetic polymers to silk fibroin-based biomaterials – could allow a suitable setting of bio-microelectrosensors inside the mentioned bladder/rhabdosphincter tissue-engineered complex [34].

Conclusive remarks

Though the bladder augmentation enterocystoplasty today remains the gold standard of surgical options for the treatment of neurogenic bladder, however the alternative tissue engineering-based approach to rebuild a functional bladder, has the advantage of avoiding the intestinal segment use-related complications [11-14,31,32,37,38].
Recent advances in the field of tissue engineering technologies make more and more validable, indeed, their applications for the augmentation cystoplasty in patients with neurogenic bladder, with foreseeable developments regarding the fabrication of suitable devices to overcome the neurogenic bladder-dependent detrusor-rhabosphincter dyssynergia. The nanotechnologies are quickly opening considerable chances in tissue engineering by allowing the control of neotissue growth and morphogenesis at nano-levels, the nanostructured "smart" synthetic polymer-based scaffold surfaces mimicking, indeed, the ECM microarchitectural conformation [39-41].
Nevertheless, just as regards the still sheerly imaginative perspective of neobladder/rhabdosphincter tissue engineered complex, its feasibility is, at the moment, questionable, given its foreseeable difficulties to properly support a bladder-sphincter physiological synergic coordination together with micturition proper device-mediated voluntary activation. It is firmly agreed on this point that to actually reach favourable purposes in the field of tissue engineering – both in the experimental and clinical transplantation surgery – it is necessary to closely keep to highly rational criteria, clearly proved in really interesting studies [42].
Particular *bioreactors,* as dynamic specific cell culture pivotal tools, can provide different biomaterial-based "seeded" scaffolds with bladder tissue mechanical-functional properties, such as elasticity and compliance towards various filling pressure values, so it allowing scaffold conformational adaptive changes under various individual conditions [24,43].
Intriguingly, quite out of synthetic biomaterials, Bombix mori (or even spider) *silk fibroin*-made scaffolds, functionalized with ECM-protein coatings, have been recently tested, in a animal model, as templates for urothelial/smooth muscle cell-seeded bladder tissue engineering, so-built augmentation cystoplasty showing both compliance- and filling pressure cystometry-assessed acceptable values [27,28].
Moreover, tissue engineering research is more and more properly intended to identify, among the dynamic reciprocity-related microenvironmental cell/scaffold interactions, possible dangerous conditions that may be due to synthetic polymer-based scaffold toxicity (phlogogenic-, carcinogenic, immunoreactive effects) and, on the other hand, to try out innovative more harmless technological modalities such as that to rebuild a reliable bladder by scaffold-less autologous smooth muscle cell sheet engineering [37,44-48].

Riassunto

Se, pur con l'adozione di trattamento precoce della dissinergia detrusoriale-sfinterica da vescica neurologica, mediante "cateterismo pulito intermittente" associato a farmacoterapia (anticolinergici, agonisti adrenorecettoriali β3), non si ottiene la stabilizzazione di adeguata *compliance* vescicale, onde prevenire l'insorgenza di danno renale, il rilievo diagnostico, in tale circostanza, di eccessivi livelli pressori vescicali in fase di riempimento e di elevato rapporto tra pressione vescicale in fase minzionale e valori uroflussometrici a causa dell' intensa resistenza uretrale, confermata, per giunta, dall'alterato reperto elettromiografico rabdosfinterico, rende necessario il ricorso a provvedimenti chirurgici, tra cui – a parte l'applicazione di stent uretrale a livello sfinterico o, alternativamente, l'iniezione intrasfinterica di tossina botulinica o, talora, la sfinterotomia, ed, inoltre, eventuale intervento antireflusso vescico-ureterale – merita particolare considerazione la cistoplastica di ampliamento vescicale con utilizzo di un segmento intestinale riconfigurato o di una porzione di stomaco, in quanto costituisce la soluzione migliore al fine d'ottenere incremento di capacità del neo-assetto vescicale con accettabili valori di *compliance.* Purtroppo a tale intervento possono conseguire severi squilibri metabolici sistemici (tra cui, acidosi ipercloremica, ipopotassiemia, demineralizzazione ossea, iperossaluria, ipocalcemia, carenza di vit. B12 ed acido folico) assieme a ricorrenza di calcolosi entero-protesica da sovrapproduzione reattiva di muco intestinale, oltre che, talvolta, insorgenza, su base patomorfosica, di neoplasie specie a livello della linea di sutura enterovescicale. Ne è derivata, pertanto, l'opportunità di ricorrere alla ingegneria tessutale onde disporre di tessuto appropriato ai fini della cistoplastica di ampliamento, quanto è stato coronato da successo clinico proprio in soggetti affetti da vescica neurologica congenita, dovuta a disrafismo spinale/ mie-

lodisplasia, o acquisita a causa di traumi spinali. Tuttavia, pure l'assetto vescicale ottenuto con ricorso all'ingegneria tessutale – alla pari dell'entero-cistoplastica d'ampliamento – rimane funzionalmente condizionato dall'afferenza di aberranti segnali nervosi ad origine dalla lesione midollare-spinale, con persistenza, pertanto, della dissinergia vescico-sfinterica. Risulta, quindi, sempre più rilevante il proposito di superare tale situazione mediante dispositivi innovativi possibilmente realizzabili con ulteriori affinamenti dell'ingegneria tessutale.

References

1. Bauer SB: *Neurogenic bladder: etiology and assessment.* Pediatr Nephrol, 2008; 23:541-51.

2. Merello E, Mascelli S, Raso A, et al.: *Expanding the mutational spectrum associated to neural tube defects:literature revision and description of novel VANGL 1 mutations.* Birth defects Res A Clin Mol Teratol, 2015; 103:51-61. doi:10.1002/bdra.23305.

3. Utomo E, Groen J, Blok BF: *Surgical management of functional bladder outlet obstruction in adults with neurogenic bladder dysfunction.* Cochrane Database Syst Rev, 2014. May.doi:10.1002/14651858.CD004927.

4. Verpoorten C, Buyse GM: *The neurogenic bladder: Medical treatment.* Pediatric Nephrol, 2008; 23:717-25.

5. Caremel R, Cornu JN, Kerdraon J, et al.: *Drug therapy of bladder dysfuncion.* Progr Urol, 2013; 23:1271-86.

6. Woodward S: *Community nursing and intermittent self-catheterization.* Br J Community Nurs, 2014; 19:388-93.

7. Miyazato M, Sugaya K, Saito S, et al.: *Suppression of DSD by herpes simplex virus vector mediated gene delivery of glutamic acid decarboxylase in spinal cord injured rats.* J Urol, 2010; 184:1204-10.

8. Hodges SJ, Yoo JJ, Mishra N, Atala A: *Effect of epigenetic therapy on congenital neurogenic bladders:a pilot study.* Urology, 2010; 75:868-72.

9. Vainrib M, Reyblat P, Ginsberg DA: *Long-term efficacy of repeat incisions of bladder neck/external sphincter in patients with spinal cord injury.* Urology, 2014; 84:940-45.

10. Mahfouz W, Corcos J: *Management of detrusor/external sphincter dyssynergia in neurogenic bladder.* Eur J Phys Rehabil Med, 2011; 47:639-50.

11. Zhang P, Yang Y, Wu ZL, Zhang N, Zhang CH, Zhang XD: *Long-term follow-up of sigmoid bladder augmentation for low-compliance neurogenic bladder.* Urology, 2014; 84:697-701.

12. Mingin GC, Baskin LS: *Surgical management of neurogenic bladder and bowel.* Int Braz J Urol, 2003; 29:53-61.

13. Schlomer BJ, Copp HL: *Cumulative incidence of outcomes and urologic procedures after augmentation cystoplasty.* J Pediatr Urol, 2014. 10:1043-50.doi:10.1016/j. jpurol.2014.03.007.

14. Alberti C: *Metabolic and histological complications in ileal urinary diversion. Challenges of tissue engineering technology to avoid them.* Eur Rev Med Pharmacol Sci, 2007; 11:257-64.

15. Atala A, Vacanti JP, Peters CA, Retik AB, Mandell J, Freman MR: *Formation of urothelial structure in vivo from dissociated cells attached to biodegradable polymer scaffold in vitro.* J Urol, 1992; 148:658-62.

16. Langer R, Vacanti P: *Tissue engineering.* Science 1993; 260:920-26.

17. Atala A: *Tissue engineering in urologic surgery.* Urol Clin North Am, 1998; 25:39-50.

18. Yoo JJ, Meng J, Oberpenning F, Atala A: *Bladder augmentation using allogenic bladder submucosa seeded with cells.* Urology, 1998; 51:221-23.

19. Atala A: *New methods of bladder augmentation.* BJU International, 2000; 85:24-34.

20. Zhang Y: *Bladder reconstruction by tissue engineering with or without cells.* J Urol, 2008; 180:10-11.

21. Del Gaudio C, Vianello A, Bellezza G, et al.: *Evaluation of electrospun bioresorbable scaffold for tissue-engineered urinary bladder augmentation.* Biomed Mater, 2013. do:10.1088/ 1748-6041/8/4/045013.

22. Shakhssalim N, Rasouli J, Moghdasali R, Adhdas FS, Naji M, Soleimani M: *Bladder smooth muscle cells interaction and proliferation on PCL/PLLA electrospun nanofibrous scaffold.* Int J Artif Organs, 1013; 36:113-20.

23. Kress S, Neumann A, Weyand B, Kasper C: *Stem cell differentiation depending on different surfaces.* Adv Biochem Eng Biotechnol, 2012; 126:263-83.

24. Murphy SV, Atala A: *Organ engineering, combining stem cells, biomaterials and bioreactors to produce bioengineered organs for transplantation.* Bioessays, 2013; 78:954-60 .

25. Mahfouz W, Elsamy S, Corcos J, Fayed AS: *Fundamentals of bladder tissue engineering.* Afr J Urol, 2013; 19:51-57.

26. Alberti C: *About recent developments of synthetic polymers for a suitable cell adhesion/ growth support in tissue engineering-based either augmentation cystoplasty or neobladder.* Ann Ital Chir, 2014; 85:309-16.

27. Chung YG, Algarrahi K, Franck D, et al.: *The use of bi-layer silk fibroin scaffolds and SIS matrices to support bladder tissue regeneration in a rat model of spinal cord injury.* Biomaterials, 2014; 35:7452-59.

28. Yu Q, Sun C: *A 3D-multiporous fibrous scaffold fabricated with renerated spider silk protein/poly (l-lactic acid) for tissue engineering.* J Biomed Mater Res A, 2015; 103:721-29.

29. Atala A, Bauer S, Soker S, Yoo J, Retik S: *Tissue engineered autologous bladders for patients needing cystoplasty.* Lancet, 2006; 367:1241-46.

30. Yoo JJ, Olson J, Atala A, Kim B: *Regenerative medicine strategies for treating the neurogenic bladder.* Int Neurourol J, 2011; 15:109-19.

31. Zhang F, Liao L: *Tissue engineered cystoplasty augmentation for treatment of neurogenic bladder using SIS: An exploratory study.* J Urol, 2014; 192:544-50.

32. Song L, Murphy SV, Yang B, Xu Y, Zhang Y, Atala A: *Bladder acellular matrix and its use in bladder augmentation.* Tissue Eng Part B, rev, 2014; 20:163-72.

33. Carone R, Bodo G, Vercelli D, Bertapelle P: *Urologic neurosurgery.* In: Carone R (ed) *Autonomous dysfunctions.* Turin: Pantè Editions, 1994; 75-83.

34. Alberti C: *A foreseeable tissue engineered approach to overcome the neurogenic bladder related detrusor/urethral rhabdosphincter dyssynergia.* Front Pediatr, 2014. doi:10.3389/ fped.2014.00122

35. Hou S, Rabchevsky AG: *Autonomic consequences of spinal cord injury.* Compr Physiol, 2014; 4:1419-53.

36. Alberti C: *Vescica neurologica* In: Bezzi E (ed). *Urologia.* Torino: UTET, 1974; 705-716.

37. Zhang C, Murphy SV, Atala A: *Regenerative medicine in Urology.* Semin Pediatr Surg, 2014; 23:106-11.

38. Lewis JM, Cheng EY: *Non-traditional management of the neurogenic bladder: Tissue engineering and neuromodulation.* Sci World J, 2007; 17:1230-41.

39. Yang B, Zhou L, Peng B, Sun Z, Dai Y, Zheng J: *In vitro comparative evaluation of recombinan growth factors for tissue engineering of bladder in patients with neurogenic bladder.* J Surg Res, 2014; 186:63-72.

40. Lu T, Li Y, Chen T: *Techniques for functional construction of 3D-scaffold for tissue enginnering.* Int J Nanomedicine, 2013; 8:337-50.

41. Yao C, Hedrick M, Pareek G, Renzulli J, Haleliban G, Webster J: *Nanostructured polyurethane -poly-lactic-co-glycolic acid scaffolds increase bladder tissue regeneration in vivo study.* Int J Nanomedicine, 2013; 8:3285-96.

42. Picardi N: *Chirurgia sperimentale e dei trapianti d'organo:storia, metodologie e conquiste tecnologiche.* Salus-Collana di Scienze della Salute. Roma: Edizioni Aracne, 2013.

43. Wei X, Li DB, Xu F, Wang Y, Zhu YC, Wang KJ: *A novel bioreactor to stimulate urinary bladder functional tissue engineering.* Chin Med J, 2011; 124:568-73.

44. Cooperstein MA, Canavan HE: *Assessment of cytotoxicity of (N-isopropyl acrylamide) and poly (N-isopropyl acrylamide)-coated surfaces.* Biointerphases, 2013; 8:19. doi:10.1186/1559-4106.

45. Domingues RM, Gomes ME, Reis RL: *The potentials of cellulose nanocrystals in tissue engineering strategies.* Biomacromolecules, 2014; 15:2327-46.

46. Talab S, Kajbafzadeh M, Elmi A, et al.: *Bladder reconstruction using scaffold-less autologous smooth muscle cell sheet engineering: Easy histological outcomes for autoaugmentation cystoplasty* . BJU Int, 2014; 114:937-45.

47. Lan Van Ba O, Aharony S, Loutochin O, Coros J: *Bladder tissue engineering: A literature review.* Adv Drug Deliv Rev, 2015; 82:31-37.

48. Mauney JR, Adam RM: *Dynamic reciprocity in cell-scaffold interactions.* Adv Drug Deliv Rev, 2015; 83:77-85.

Commento e Commentary

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Trattasi di una revisione storica, ben esposta in modo chiaro e completo, delle principali problematiche, soprattutto terapeutiche, correlate alla presenza di una vescica neurogena da dissinergia vescico-sfinterica. L'aspetto di maggiore attualità è quello relativo all'utilizzo di biomateriali sintetici per l'ampliamento vescicale quando esista indicazione a questo tipo di intervento. La proposta, anzi l'idea, presentata dall'Autore, di costruire una vescica cosiddetta "intelligente", capace cioè di attivare meccanismi funzionali (rilasciamento, contrattura, compliance) appare assolutamente entusiasmante. Qualche piccolo segnale applicativo a livello sperimentale è già apparso nella letteratura internazionale, soprattutto utilizzando biomateriali funzionalmente ancora più simili al tessuto vescicale normale con possibilità di contenere bio-micro-elettrosensori attivabili dall'esterno. La strada è comunque lunga e difficile ma verosimilmente appare la più indicata per trovare una soluzione terapeutica ottimale ad una patologia urologica (congenita ed acquisita) così invalidante dal punto di vista fisico e psicologico.

* * *

The paper is a clear and comprehensive historical review of the main therapeutical issue related to problems of neurogenic bladder affected by bladder-sphincter dyssynergia.
The more actual hope is about the possibility of using synthetic biomaterials for bladder augmentation when there is indication to this type of reparative procedure. The author's proposal, or better his idea, to build a so-called "intelligent" bladder, that means be capable of activating functional mechanisms (relaxation, contracture, compliance), is absolutely exciting. Some small previous experimental applicative examples in this field has already appeared in the international literature, especially using biomaterials functionally more similar to normal bladder tissue, with possibility of containing bio-micro-elettrosensors driven from the outside.
It is a difficult and still long road to go through, but probably it appears to be the more desirable project for realising an appropriate and optimal therapeutic solution for a urologic pathology, that is so debilitating in terms of physical and psychological consequences, whether congenital or in acquired eveniences.