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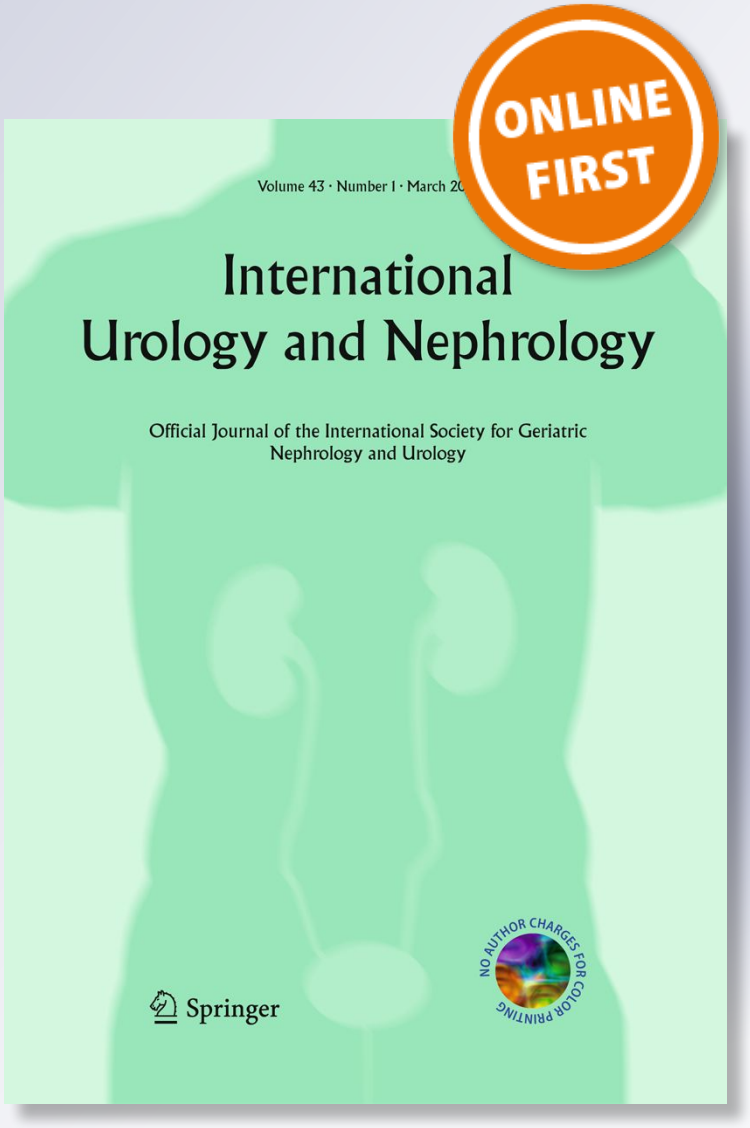

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UROLOGY - REVIEW

Alloplastic bladder substitution: are we making progress?

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Abstract Radical cystectomy with lymphadenectomy and urinary diversion is the gold standard treatment for bladder cancer in organ-confined muscle-invasive disease and selected patients who have high-grade non-muscle-invasive disease or are non-responders to BCG. The main and most morbid complications of this challenging surgery are related to the use of bowel for urinary tract reconstruction. For this reason, many past projects were devoted to finding an alternative to the use of bowel. The aim of this review is to provide a summary of the evolution of alloplastic bladder substitution. A comprehensive review of the literature was performed using the Medline National Library of Medicine database and Google Scholar. Keywords used were cystectomy and intestine/bowel, replacement, bladder substitution, organ replacement, artificial bladder, alloplastic material, biomaterial, and tissue engineering. Various prostheses have been proposed for replacement of the urinary bladder, silicone being the most frequently used material. The first published model of an alloplastic bladder was described by Bogash et al. in late 1959, while the last, in 1996, was suggested by Rohrmann. Interprofessional collaboration, recent advances in technology, and tissue engineering may help in developing suitable bladder prostheses. Urologists as well as engineers and the industry need to give this matter serious attention.

Keywords Urinary tract · Transplantation · Silicone · Scaffold · Bladder tissue engineering · Bladder

Introduction

In the Western world, bladder cancer is the fourth most common malignancy in men and the eight most common in women, with more than 330,000 new cases and more than 130,000 deaths per year. It represents the most common malignancy of the urinary tract, with a peak incidence in the adult and elderly population, and at any point in time, 2.7 million people worldwide have a history of urinary bladder cancer [1–3]. Although the majority of patients present with superficial bladder tumors, 20–40 % either present with or develop invasive disease. Radical cystectomy with pelvic lymph node dissection is the gold standard treatment for organ-confined muscle-invasive disease, and it is also a valid option for selected patients with high-grade non-muscle-invasive bladder cancer, either as a primary treatment modality or for recurrent or refractory tumors after bladder-conserving regimens. However, this procedure, which

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is performed with a curative intent also in the elderly population [4, 5], is complex, involving simultaneous surgery on the urinary and gastrointestinal tracts, and is associated with a high rate of complications (17–66 %) and morbidity [6–8], with prolonged hospital stay and potential readmission. The complications are generally considered to be primarily attributable to the urinary tract reconstruction (UTR), which relies on sampling of bowel to restore urinary bladder function. Such complications have an effect on the patient's physical and psychological well-being and increase significantly the total cost of the intervention. Since we are facing a rise in life expectancy [9], with increases in both the elderly and the bladder cancer population, treatment management in these patients represents an important challenge for present and future urology.

The function of urinary bladder is to store urine at low pressure and to permit voluntary voiding without involuntary leakage of urine; so, from a mechanical point of view, it can be considered a sophisticated waterproof reservoir which fills and empties at low pressure [10].

Since the first cystectomy for bladder tumor, performed in 1887 by Bardenheuer in Cologne, appropriate replacement of bladder function and reduction in the impact of cystectomy on the patient's quality of life (by maintaining control over voluntary voiding and continence, preserving renal function, and ensuring that UTR is esthetically acceptable) have become the main surgical challenges. Because of the impossibility of replacing the bladder with a transplanted one (allograft or xenograft), surgeons and researchers have sought alternative solutions for UTR that avoid the use of bowel tissue. The idea of replacing bladder with a synthetic prosthesis, thereby obviating the need for use of bowel and the associated numerous complications, has always been attractive and the source of investigation [11–37].

Recent initiatives in the development of biomaterials for organ replacement or functional reconstruction include alloplastic, biologic, and bioengineered biomaterials. Nowadays, urinary bladder substitutes can be divided into *biologic* and *alloplastic*. Biologic ones are all urothelial substitutes that originate from or have been synthesized or developed from living organisms, while alloplastic ones can be simply defined as all non-biologic materials.

Over the last two decades, advances in regenerative medicine, cell and stem cell biology, material sciences, and tissue engineering have enabled researchers to develop cutting-edge technology leading to the "construction" of different tissues [11–20]. Within urology, interest has in particular focused on development of a urothelium substitute for bladder, ureter, and urethra replacement. Regarding urinary bladder replacement, the subject of this paper, many groups have worked with cultures of regenerated multilayer urothelium, the group of Atala having been the first to publish on an "engineered bladder tissue created with autologous cells usable for a cystoplasty" [12]. However, while preliminary results on urothelial substitutes and the first biologic neo-bladders seemed promising, discouraging drawbacks emerged such as cell mutations, biodegradability of the scaffold, the lack of direct vascular supply, disappointing long-term outcomes of the "transplanted" new organ, and continuing high costs; taken in conjunction with ethical and oncologic considerations, these limitations illustrated the need for further advances [14–20].

Alloplastic materials, on the other hand, have progressively entered the daily clinical practice of every specialty. Urology, in particular, would not be the same without devices such as bladder and ureteral catheters. Since the Egyptians first used the stalk of papyrus to drain urine thousands of years ago [21], alloplastic materials have gradually become more useful, comfortable, and cheaper. However, while in most specialties the use of permanent implants is possible (e.g., articular or vascular prostheses), in urology this does not seem feasible as yet owing to infections and encrustations that result from the continual exposure to urine.

The main aim of this study is to analyze data published on non-bowel, alloplastic bladder substitution, summarizing the evolution, the current situation, and the most relevant findings.

Materials and methods

A comprehensive review of the literature was performed using the Medline National Library of Medicine database and Google Scholar. We considered suitable for our review all historical models of bladder substitution without the use of bowel, emphasizing the alloplastic models. The review included articles published between January 1, 1958, and September 1, 2011. Only articles in English were considered suitable for the study. Key words used were cystectomy

Table 1 Main models of alloplastic neo-bladders

Model (ref.)	Innovative features	Species	Main complications
Bogash [22]	1st model; silicone reservoir; external connection for drainage of urine	25 Dogs	Hydroureteronephrosis, renal failure, and UTIs due to external connection
Friedman [23]	Thin-walled collapsible reservoir	Dogs	Connective tissue deposition, alteration in dynamic properties, renal failure
Abbou, Auvert, Apoil and Vacant models [24–27]	Ovoid silicone reservoir, mechanical voiding system with urethral sphincter	Dogs	Connective tissue deposition, alteration in dynamic proprieties
Stern [28]	Silicone reservoir with external strips (anchored system)	32 Dogs	Progressive renal failure due to papilloma formation
Kline and Belden models [29, 30]	Bistable prostheses (rigid base and flexible top)	Dogs	Connective tissue deposition, alteration in dynamic proprieties
Gurpinar [34]	Bi layered prosthesis, interposition of ileal reservoir, external connection to drain urine	Dogs	Abundant residual volume, UTIs, encrustations
Mayo Clinic [35, 36]	Sophisticated reservoir with a mechanical system for filling and emptying	4 Dogs	Multiple technical failure
Aachen [37]	2 subcutaneous compressible reservoirs that drained into urethra through a "Y" form tube	Sheep	Urinary leakage from sites of anastomosis, not reproducible in humans

UTI urinary tract infection

and intestine/bowel, replacement, bladder substitution, organ replacement, artificial bladder, alloplastic material, biomaterial, and tissue engineering. Research was directed at all forms of urinary bladder substitute, whether biologic or alloplastic. Aspects analyzed included the following: the kind(s) of material used for prosthesis; technical features of the prosthesis; the mechanism of urine storage and voiding; the system used to achieve continence; the type of anastomosis between the prosthesis, ureters, and urethra; the type of suture used for prosthesis implant; the system of prosthesis fixation; whether implantation was performed in humans or animals; the species of animal used for implantation; the number of prostheses implanted for each author/group; complications after prosthesis implantation; causes and effects of complications; time until presentation of complications; death after prosthesis implant; possibility of repair or substitution after implant; and durability of prosthesis.

In total, 73 articles published in 23 journals were included in the review and then further selected according to the author.

In the last 50 years, many different prostheses have been proposed for replacement of the urinary bladder, silicone being the most widely used material. The most common models described include the following: plastic reservoirs and mechanical valves with abdominal drainage of urine via a silicone tube [22, 23], a silicone rubber prosthesis with transurethral drainage of urine [24], a bistable latex prosthesis [25], and a silicone rubber reservoir and artificial urethra equipped with a sphincter [26]. A variety of other prostheses have been investigated during the past 53 years [27–37], with the most complex being those described by the Mayo Clinic group [36] and Rohrmann et al. [37] in 1992 and 1996, respectively (Table 1). Below we describe and analyze the most "popular" alloplastic implants.

Main alloplastic models

(1) The *Bogash model*: In this first model of artificial bladder, presented in the late 1960s by the pioneers in alloplastic substitution of the urinary bladder (M. Bogash, F.P. Kohler, and R.H. Scott), ureters drained into a silicone tube connected to the external abdominal wall. The prosthesis was implanted in 25 dogs divided into three groups according to the urinary diversion performed, the kind of ureteral reimplant, suture, and positioning of the bladder prosthesis.

Main issues: Hydroureteronephrosis due to retractile scarring occurred at sites of ureteral anastomosis, and urinary infections arose secondary to the external connection. The prosthesis lasted for 4 weeks [22].

(2) The *Friedman model* [23] was a prosthesis created to store an acceptable volume of urine without an increase in intravesical pressure; it consisted of a thin-walled collapsible neo-bladder with a storage volume of 250 ml. Ureters and urethra were directly anastomosed to the prosthesis. All animals developed hydroureteronephrosis within 2 weeks of implant.

Main issue: Deposition of connective tissue around the prosthesis interfered with the dynamic properties of the device, with subsequent hydroureteronephrosis and renal failure.

(3) The *Abbou model* [24] (Fig. 1) and contemporaneous French models [25–27] employed an ovoid reservoir originating from a basic silicone rubber prosthesis with a capacity of 200–600 ml and equipped with a mechanical voiding system. In these models, orthotopically placed ureters were connected with the posterior surface of the prosthesis and included antireflux valves; the urethra was equipped with a sphincter. Alloplastic ureters and urethra were anastomosed to the native ones, and the command mechanism and connecting tube were implanted near to the iliac crest. Tissue–prosthesis connections were achieved using a porous biomaterial or polyethylene glued to the silicone. Clinical research was performed on dogs; each dog was killed, and histologic analysis of the neo-bladder was performed to determine the "tolerance" to the prosthesis.

Main issues: A thick fibrous capsule was found to have progressively formed around the prosthesis, interfering with the dynamic properties of the devices (expansion and emptying); furthermore, progression to hydronephrosis and renal failure was documented in each dog.

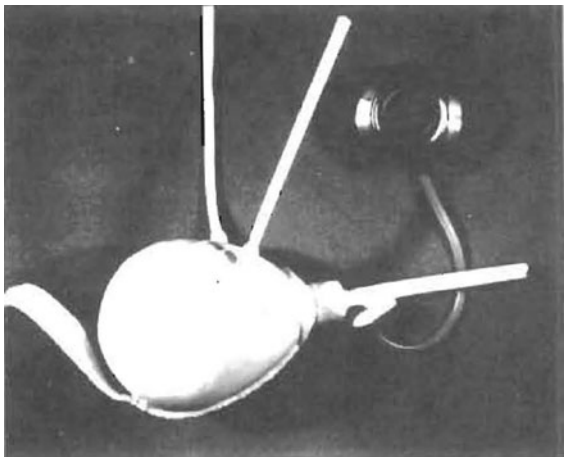

Fig. 1 One of the oldest alloplastic neo-bladders, the Abbou model: an ovoid prosthesis with its urethral sphincter (from reference [24])

(4) The *Stern model* [28] was a 200 ml total silicone prosthesis externally equipped with Dacron strips to anchor the reservoir to the retroperitoneal space. It was implanted in a total of 32 dogs.

Main issues: Hydroureteronephrosis and renal failure occurred due to urinary obstruction caused primarily by the intraluminal formation of papillomas at the ureteroprosthetic junction, probably as a result of the presence of pure silicone.

(5) The *Kline model* [29] (Fig. 2) was a bistable latex prosthesis with hydrogel lining the surface. It was implanted in the pelvic region, and emptying was provided by gravity, the weight of abdominal organs, and pressure caused by muscular tension in the abdominal wall. The *Belden* model [30] was a similar bistable prosthesis (with a rigid base and flexible top) tested in late 1990. The implanted prostheses were observed to void completely with a constant flow rate of 7–9 ml/s. The experiments were conducted on dogs, and functional results were achieved within quite a short time (9 days in the case of the Kline model), but no further analyses were done because problems similar to those mentioned above were foreseen in longer follow-up.

(6) The *Rigotti model* [31] and then the *Gleeson model* [32] were fixed-volume reservoirs designed to exceed, with their rigid scaffold, compressive forces resulting from connective deposition on the prosthesis and to reduce the risk of hydroureteronephrosis and renal failure. Emptying and voiding were allowed by an external air pump connected with the device.

Main issues: Infections occurred in association with the external connection, and cosmetic results were not good.

(7) The *Lutzeyer model* [33] was a single-chamber silicone prosthesis that rebounded to its original form after external compression. It was implanted in 17 sheep and worked well in approximately 50 % of them for about 7 months.

Main issue: The prosthesis was of limited use in humans because of the required subcutaneous implantation for compression.

(8) The *Gurpinar model* [34] was a fixed-volume reservoir anastomosed to native urethra and composed of two parts: an internal part made of silicone rubber

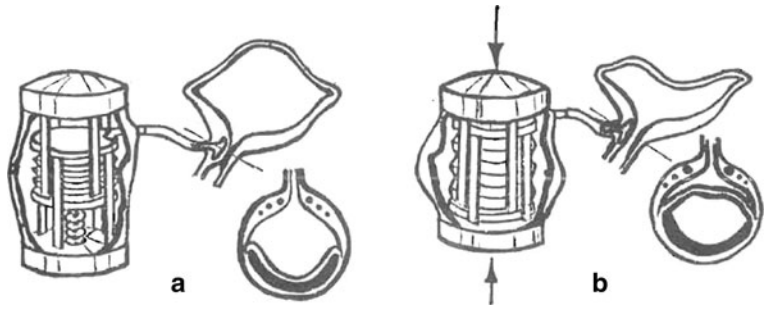

Fig. 2 The Kline model. Views of a urethral valve: **a** valve closed; **b** valve opened by manual pressure (from reference [29])

for urine and an external part made of a polytetrafluoroethylene polymer. It was hoped that this dual composition would avoid fibrous capsule formation that could be responsible for dynamic alteration in the device. Ureters were anastomosed to an ileal reservoir that was then connected to the prosthesis. This device needed an external connection to the abdominal wall to ensure anterograde drainage through the urethra.

Main issues: Infections due to the external connection, abundant residual volume of urine, ureteral dilatation due to chronic reflux, encrustation, and stone formation were the main causes of failure of this sophisticated device.

(9) The *Mayo Clinic model*, presented by O'Sullivan et al. [35, 36], was among the most sophisticated of the proposed models and was based on negative pressure drainage of urine from kidneys and active voiding. It consisted of two different shells: An inner one of silicone (230 ml) was surrounded by an external one of polysulfane (300 ml). Both were connected to the bladder neck with a 70-ml space between them. An internal spring mechanism generated negative pressure when compressed, facilitating filling, and a similar pressurized mechanism facilitated voiding. Ureters were intubated with an 8-Fr silicone catheter reinforced with a nylon spiral, and the prosthesis drained under positive pressure into a silicone tube inserted into the urethra. Watertight anastomosis was ensured by Dacron reinforcement at anastomosis sites. The prosthesis was implanted in four dogs.

Main issues: This overly complex model failed inexorably within a few weeks because of infections and the technical failure of various components.

(10) The so-called *Aachen model*, described by Rohrmann et al. [37], was another complex device and had the "longest" durability to date (>18 months in two sheep with no technical problems) (Fig. 3). It consisted of two separated subcutaneous and compressible elastic reservoirs, which drained urine from each kidney via a Dacron-covered silicone tube placed through the renal parenchyma like an "artificial ureter." Both reservoirs drained into the urethra through the interposition of a silicone tube with a "Y" form; external compression caused the positive pressure useful for voiding, with contemporaneous negative pressure within the reservoir to increase filling.

Main issue: Urinary leakage occurred owing to material failure (Dacron) at the anastomosis sites.

All of the above prostheses were of silicone or silicone based; none was implanted in humans (all were implanted in dogs or sheep), and none presented acceptable durability as a precursor to human application. Since the very first model, with few exceptions, meticulous monitoring of prosthesis function was undertaken, including the performance of urography and cystography. All animals were killed, and the prosthesis and host tissue were analyzed by a pathologist either at the end of the experiment or beforehand in the event of death or complications. None of the papers reviewed analyzed the cost of using the prosthesis for bladder replacement. An evaluation of costs of experimentation and the economic benefit that would derive from the ideal bladder prosthesis have, however, been undertaken relatively recently by McAteer et al. [38]. Conclusions of this interesting paper are that if the market sizes are deemed large (considering the number of patients treated per year), it could be worth proceeding with development of a new prosthesis.

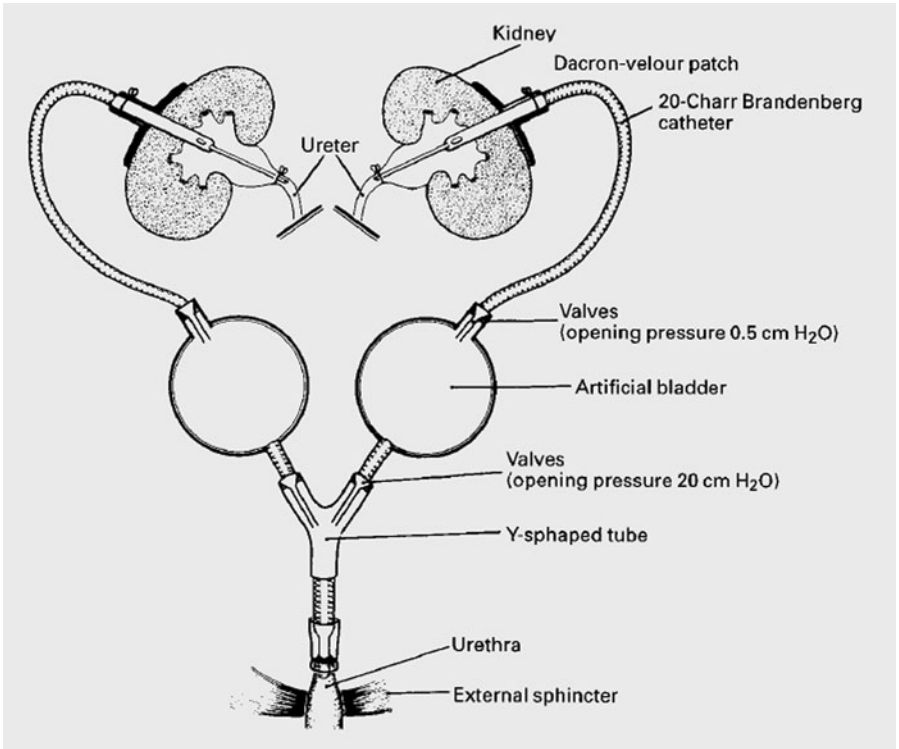

Fig. 3 The last alloplastic neo-bladder published: the Aachen (Rohrmann) model. Schematic view of two artificial bladders as they were implanted in sheep (from reference [37])

Discussion

As highlighted by the described results, many have already attempted to develop the ideal alloplastic neo-bladder, but without success. As mentioned above, the main causes of the failure of all these models were as follows: deposition of connective tissue, encrustations, infections, hydroureteronephrosis, leakages of urine from urethral or ureteral anastomosis, and problems related to biocompatibility. As regards the last mentioned, silicone has been the most widely used material, but it has been shown that silicone is not the ideal material for bladder substitution because of its low resistance to infection and encrustation. A critical and careful analysis of all the causes of failure as listed by Desgrandchamps and Griffith [39] might permit extrapolation of fundamental data and development of guidelines for future models. Ideally, a well-functioning reservoir for urine should be totally biocompatible and impermeable, have the capacity to store a sufficient volume of urine, permit filling and voluntary voiding without any pressure repercussions in the upper urinary tract, avoid any leakage of urine, resist encrustation and infection, be simple to implant and simple to remove/replace in the event of malfunction, and have an acceptable duration and cost.

Most of the results obtained with the biologic and bioengineered biomaterials are purely experimental. Although some promising results have been obtained, no biomaterial is currently available to replace bowel tissue. Such biomaterials may play a role in the future of organ replacement, but, unfortunately, results are still far from sufficiently compelling to warrant their daily use in urology. But why have so few clinical advances been made in this field of research over the last 60 years? Some of the reasons are inability to expand cells in vitro, inadequate vascularity of the implanted graft, and inadequacy of the currently available biomaterials.

A new alloplastic reservoir that meets these requirements could have enormous clinical/practical, physical, psychological, and economic benefits. The need to restore bowel function is the principal reason why duration of surgery and inpatient recovery time

are lengthy. Without the need for bowel surgery, the operation would entail simple reimplantation of ureters and urethra, easily halving the duration of surgery and the recovery time. Indirectly, this would permit a reduction in drug administration during surgery and hospitalization, thereby saving money. The resultant quicker turnover of patients would also permit a reduction in the waiting list for surgery. Furthermore, absence of use of bowel segments to restore bladder function would potentially reduce readmission for potential attendant complications. In psychological terms, an orthotopic prosthesis would also have evident benefits as regards avoidance of an external stoma [40–43]. The lack of a need for bowel surgery would permit more rapid restoration of physical activities and faster progression to adjuvant therapies on account of a better physical condition. It would also reduce the enormous economic cost incurred by every national health system owing to the following: (a) use of the instruments needed for bowel surgery (mechanical stapler, suture needles, etc.), (b) use of devices for the rest of the patient's life, such as external stoma appliances/bags (in patients with an external stoma), pads (in incontinent patients with orthotopic reconstruction), and bladder catheters (in patients performing self-catheterization), and (c) the need for subsequent interventions or readmission to hospital. Furthermore, the identification of a biomaterial that can be used as a surrogate for urothelium could be of value in the majority of pediatric pathologies that require the use of bowel (e.g., neurogenic bladder, bladder exstrophy). Such an ideal urothelial substitute could be easily tailored during surgery and used for bladder augmentation/substitution or as a graft for treatment of urethral strictures. Similarly, when the ureter is too short after ureterectomy, it could be replaced instead of doing a psoas bladder-hitch or a Boari bladder flap procedure with the attendant inherent technical difficulties and postoperative hazards. Finally, the identification of biomaterials that are resistant to infection and encrustation and have reasonable durability when in contact with urine may provide a new "family" of urologic devices, such as urethral or ureteral catheters usable in daily clinical practice.

Although the focus of this article is on complete bladder replacement with a prosthesis, it must be recognized that nowadays the functional results of urinary tract reconstructions, such as simple conduits, are acceptable and reasonably uniform. Bowel sampling for bladder substitution cannot represent the standard solution for future urology.

A critical analysis of urothelial substitutes reveals that owing to the lack of knowledge on biology, cell cultures, and tissue engineering, the first ones were totally alloplastic and silicone based, while more recently all attention has turned to the purely biologic materials. Perhaps, this is one of the key factors in our failure to achieve bladder substitution. Purely alloplastic models were tried without success, and we are still experimenting with purely biologic ones, again without significant success. Perhaps, the solution is a "hybrid" model, both biologic and alloplastic, so that one biomaterial can help to solve the problems associated with the other. Although many different alloplastic and biologic prostheses have been investigated during the past 50 years and more, the challenge of replacing this "simple" organ remains. While technical designs have become more sophisticated and new biomaterials with higher biocompatibility are now available, we are still looking for a real alternative to bowel sampling.

We hope that collaboration between urologists, engineers, biologists, and biomaterialists, with the incorporation of recent developments and know-how in tissue engineering, will lead to technical and practical remedies to previous problems and the identification of all the features required for the ideal bladder prosthesis. Whether or when a biomaterial with the above-described properties will become available for commercial and medical use remains an open question given past disappointments.

Conclusion

The pool of patients affected by bladder cancer is increasing, at least in part because of the rise in life expectancy. Radical cystectomy is the gold standard treatment for muscle-invasive bladder cancer, and bowel sampling for bladder substitution is still the only reconstructive alternative for such patients. Although artificial substitution of the bladder would be desirable owing to the physical, psychological, technical, and economic benefits, an alloplastic material with properties compatible to the human body has yet to be discovered. So, the answer to the question proposed in the title ("Are we making progress?")

must be either an unequivocal "no" or "insufficient." Indeed, the repeated failure of this therapeutic approach has been one of the factors prompting researchers to explore tissue engineering and other alternatives to conventional enterocystoplasty. Interprofessional collaboration, recent advances in technology, and innovations in tissue engineering may help in developing a suitable alloplastic or bioartificial prosthesis. Urologists, engineers, and industry all need to give this matter serious attention.

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