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Bladder Replacement

The normal urinary bladder is a most adaptive organ. It has an amazing ability to stretch and fill the fatty pelvic space that surrounds it. It has the quality of compliance, which means it can increase in volume a lot and not increase its pressure. The receptors (sensory nerve endings) in its wall, ultimately connected to the brain, have, under usual conditions, a high threshold for sending a signal that urination is imminent; they remain "silent" most of the time, allowing us to go about our business, or sleep without the inconvenience of finding a restroom. As the bladder expands, its wall gets thinner but has enough elasticity and "substance" that rupture is rarely seen, as it might be in a distended intestine. To some extent, the full bladder will compress the ureters (tubes entering it from kidneys) to slow down its own further expansion with urine. The volitional signal from one's brain to the bladder to urinate causes variable contraction of the "smooth" muscle tissue spherically encompassing the bladder and relaxation of pelvic floor "skeletal" muscles to allow rapid and complete evacuation. The neurophysiology and complex "integrated circuitry" that balances bladder storage and emptying is not totally understood, although what is known is the basis for drugs that influence and improve bladder function.

<u>When the bladder has to be removed (cystectomy),</u> such as in cases of muscle invasive or less invasive but refractory and/or symptomatic bladder cancers, replacing it in its native location with biological tissues if a far better solution than a urinary ostomy (= urostomy, urine coming into bag on abdominal wall) although not suitable in all situations. Most

so-called “neo”-bladders take longer to construct, and add length to an already demanding operation--often done on older patients with significant medical conditions. Patients undergoing the procedure need to have good renal function to avoid the issue of reabsorption, through the lining of the intestinal bladder replacement, of chemical waste products. Pre-existing urinary leakage would be a reason to give 2nd thought. A bladder replacement patient must accept the surgical consequences, in advance, including a high percentage of leakage at night, much lower percentage of leak associated with coughing/laughing/exercising (stress incontinence) during the day, and the possible need to do self-catheterization many times daily, perhaps indefinitely, to mechanically empty the new substitute bladder (50% in women). When the bladder cancer is close to the prostate in men or to the urethra in women, or on the lower back wall of the bladder in women, connecting the intestinal substitute to the urethra may risk having cancer at the surgical margin, and then recurrence of cancer in the pelvis. In women, proximity of the tumor to the vagina may mandate removal of part of the vagina—that will lead to less support of the bladder and likely worse urinary control.

Requirements for a biological bladder substitute include a reservoir that (1) can hold adequate urine, preferably, as the patient recovers, close to 15 oz.; (2) is made of small intestine which works better than other gastrointestinal organs and of which there is enough (usually 17-20 inches required) to “spare”; (3) can be rendered a low pressure storage system, such as is the case with a normal bladder—a surgical technique called “detubularization” accomplishes this by changing the sausage configuration of small intestine into a long vascularized patch of tissue, which is then shaped by several suture lines to resemble the cover of a giant baseball; (4) not too much fat, and stretchability of the broad blood supply (mesentery) of the intestine so that a tension-free suturing (=anastomosis) of the neo-bladder to urethral stump can be accomplished--this will maintain good blood supply to both the neo-bladder and the area of anastomosis and will prevent neo-bladder shrinkage as well as anastomotic leaks of urine into the pelvis and scar tissue narrowing the juncture with urethra; (5) incorporation into the neo-bladder of what is called an afferent limb or a "chimney"-- a piece of the intestine (the "upper part" harvested) remaining tubularized and to which the kidney tubes (ureters) are attached so that reflux or backwards flow of urine won't occur when the bladder is full.

An intestinal neo-bladder will produce mucus, more of a problem early on postoperatively when the catheter is still in, often for 2-3 weeks; regular or "as needed' irrigation may be required to maintain proper catheter function. Some patients may need to insert a tube well after the postoperative period to help evacuate mucus that does not easily egress with the urine.

<u>As one who likes the challenges of urinary tract reconstruction and performing this type of "urinary diversion",</u> I can say that physically and psychologically, the quality of life for the bladder cancer patient is <u>much better</u> than with an ostomy. In addition, I believe that some patients may be willing to "give up" their bladder earlier in their disease, knowing that a bladder substitute is a quite reasonable albeit imperfect treatment alternative. This is important since locally advanced (into fat surrounding bladder) bladder or metastatic (spread to other organs) cancer is not uncommonly lethal, and bladder cancer may be underestimated (understaged) by transurethral biopsies even combined with MR and other imaging. For example, a patient with a

high grade (very malignant-appearing) bladder cancer may wish to consider cystectomy/neo-bladder with the 1st episode or certainly recurrence of a T1 tumor (invading into the layer between bladder lining and muscle). Likewise may be someone whose flat cancer, aka carcinoma-in-situ (CIS) or even multiple recurrent superficial cancers become refractory to transurethral therapy and topical treatment, e.g., failure of BCG, instilled into the bladder repetitively, to control the disease.

A few other words about bladder replacement. Some forward thinking researchers, such as Dr. Anthony Atala of Wake-Forest University, have gotten fairly far with <u>partial</u> bladder and urethral replacements by culturing bladder lining and muscle cells outside the body, stimulating these with so-called growth factors, "molding" these cells by using a biological scaffolding in the shape of bladder and implanting these later into the body. Bladders with cancer cannot be the source of these cells. One problematic issue here is how would an <u>entire</u> such bladder replacement get an adequate blood supply to survive, since we are not talking about a transplant, per se, in which the new organ is hooked up to the host's native blood supply. Such bladder tissue engineering can also be performed with stem cells, not only embryologic sourced ones (the "sociologically controversial" ones) but also adult stem cells and similar cells in the placenta/amniotic fluid of a newborn, which can be harvested, banked and used later for the same individual if the need arises or for a genetically similar person. Stem cells are "pluripotent", meaning they can be induced into forming the cell lines of any of multiple different bodily organs. There is even some evidence that in the future, <u>non</u>-stem cells could be induced, by genetic manipulation, to de-differentiate, that is, change their purpose and become, for example more, like a bladder than an oral cavity lining cell. The use of “synthetic” bladders, per se, in experimental settings, has met more issues of stone formation, rejection, infection, and poor function.

In bladder replacement, the future is here, and the advances over the last 25 years have taught us that urinary and kidney function can be quite good if the procedure is done competently on the right patient.

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