

Title: The use of SurgiSIS, an acellular collagen matrix, in endoscopic urethroplasty

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Declaration

I declare that this dissertation is my own work. It is being submitted to the University of Cape Town for the degree M.Med.(Urology). It has not previously been submitted for any degree or examination to any other university.

Figures 1, 4, 6 and 8 in this dissertation are copies of my own original work. Figures 2, 3, 5, 7, and 9 to 13 are copies of pictures that were kindly provided by Professor JH Naude.

Signed by candidate

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Summary

Objectives

To evaluate small intestinal submucosa (SurgiSIS) as a substitute for skin in endoscopic urethroplasty performed as treatment for inflammatory and iatrogenic strictures of the male bulbar urethra and in the early treatment of bulbomembranous urethral injuries associated with recent pelvic fractures. The tissue integration and epithelialisation of SurgiSIS used in endoscopic urethroplasty is assessed. The long term maintenance of urethral patency following this treatment form is assessed.

Patients and Methods

Nine patients with bulbar urethral strictures defined by urethrography were enrolled. Following an optical urethrotomy, the SurgiSIS grafts were tubularised over a purpose-specific graft-carrying balloon device and secured into the opened urethra as described for endoscopic urethroplasty. Patients were followed up with urethroscopy and urethrography at regular intervals as per protocol, or when symptoms arose. Failure was defined as the need for any further intervention.

Results

Two patients, both with short inflammatory strictures, maintained urethral patency without any intervention at one and two years respectively. Six patients developed stricture recurrence within six months of surgery. Three of these have undergone subsequent open urethroplasty. Two are currently awaiting urethroplasty and one is maintaining urethral patency with regular self dilatation. One patient was lost to follow-up.

Conclusion

Endoscopic urethroplasty with unseeded SurgiSIS grafts was unsuccessful in this study.

Introduction

Urethral stricture disease presents a massive challenge to health care systems in the developing world and particularly so in Sub-Saharan Africa. The demand for the effective treatment of urethral strictures far outstrips the available resources and expertise.¹ The situation in South Africa is not quite as dire as in most of the continent, but the treatment of urethral stricture disease constitutes a major proportion of the urological workload in state hospitals throughout the country.

The common causes of urethral strictures are inflammatory, traumatic and iatrogenic. Strictures most commonly occur in the bulbar urethra. Inflammatory strictures are caused by gonococcal urethritis. The most common type of trauma affecting the bulbar urethra is iatrogenic, either during transurethral procedures or related to urethral catheters. Fall-astride accidents or a kick in the perineum can injure the bulbar urethra. Pelvic fractures are associated with injury of the membranous urethra. These are distraction injuries with complete or incomplete rupture of the membranous urethra. In complete rupture there is separation between the prostatic and bulbar urethra. The resultant defect is filled by haematoma and heals with fibrosis and interposed scar tissue formation.

Urethral strictures can be treated in several different ways. In order of advancing complexity the treatment can involve blind dilatation, optical urethrotomy under direct endoscopic vision, or some form of urethroplasty. The blind dilatation or cutting of a urethral stricture is one of the oldest surgical treatments known to man. Open urethroplasty refers to the surgical repair of a stricture. This can be an anastomotic repair, where the two ends of normal urethra are spatulated and anastomosed, or some form of substitution urethroplasty where tissue from outside the urethra is introduced in the form of a pedicled flap or a free graft in order to repair the stricture. One stage procedures are generally favoured, but occasionally very complex or very long strictures need to be treated by a two-stage procedure. Endoscopic

urethroplasty involves the endoscopic placement of a graft into a strictured area of the urethra that has been cut open by optical urethrotomy.

This dissertation focuses primarily on the treatment of bulbar urethral strictures and to a lesser extent on the early treatment of post-traumatic membranous urethral injuries by means of endoscopic urethroplasty.

Figure 1 - Bulbar urethral stricture



Historical overview of the treatment of urethral strictures

Diseases of the male urethra have plagued man since ancient times. This passage in Leviticus 15 verse 2 in the old testament of the Bible is perhaps one of the earliest recorded references to urethritis: *“And Jehovah spoke unto Moses and to Aaron, saying, speak unto the children of Israel, and say unto them, when any man hath an issue out of his flesh, because of his issue he is unclean”*

Urethritis, and specifically gonococcal urethritis, was most likely the predominant cause of urethral strictures in ancient times. It is unlikely that

patients would have survived the injuries associated with pelvic fractures and iatrogenic injury must have been very rare indeed. The term gonorrhoea was possibly coined by Galen. Seneca, Aristotle, Plato and Hippocrates all commented on the disease. Celsus recorded stones impacted behind a stricture.²

The blind dilatation of urethral strictures has been practised for a very long time indeed. The Sushruta Samhita, an early Indian surgical text dated approximately 1000 B.C., described tubes of gold, silver and wood smeared ghee, a liquid butter, for the evacuation of urine, management of strictures, instillation of medicines and assistance with lithotomy.³ Tombs of ancient Egypt contained bronze bougies in case the need arose to dilate the stricture of the deceased in the afterlife.³ The early history of Western urology is largely the history of the treatment of bladder stones and urethral strictures.

Arataeus (80A.D.), a Roman physician and contemporary of Galen, refers to external urethrotomy and suprapubic puncture of the bladder with a trocar. Heliodoros describes the treatment of urethral strictures by internal urethrotomy with a pointed and sharp stiletto in his book 'Opera chirurgica'.⁴ Galen (138 to 201 A.D.) recommended a curved or S-shaped catheter. Oribasius (325 to 403A.D.) who was physician to the Emperor Julian, described urethrotomy and an indwelling catheter made from treated paper.³

The famous French surgeon Ambrose Pare from Paris used lead bougies to manage urethral strictures in the 16th century and performed internal urethrotomy, probably through a perineal incision.³ Up to the 18th century physicians had difficulty distinguishing between urethral stricture disease and prostatic enlargement as the cause of urinary retention. The anatomical drawings of Leonardo da Vinci (1452 to 1519) suggest that the anatomical understanding of the lower urinary tract was incomplete. None of his drawings displays the prostate.³

Mount Vesuvius erupted in 79 A.D. and buried Pompeii until excavation in 1748. A surgeon's house in that city revealed a variety of bronze urethral

catheters, some straight and others curved.⁵ John Hunter, the great English anatomist and surgeon, advised against forceful dilatation with bougies. He applied nitrate of silver prior to dilatation. Hunter was also the first to suggest antegrade dilatation via an opened bladder. He applied instruments from both sides of the stricture so that he could perforate it with a sharp stiletto. He also pressed a bougie against an impassable stricture for a long time, similar to the “dilatation vitale” described by Dupuytren.⁴

The late 18th and early 19th centuries saw much enthusiasm for internal urethrotomy, with more than 20 urethrotomes being described between 1795 and 1841. Tiemans *armamentarium chirurgicum* of 1876 listed 36 urethrotome models.³ In 1845 Maisonneuve described filiforms and followers, and in 1855 he described his urethrotome that could be attached to a filiform and was used into the second half of the 20th century.⁶ The American Fessenden N. Otis developed his dilating urethrotome in 1876, as quoted in Schultze-Zeeman's article on the history of internal urethrotomy.⁴

The next major development was urethrotomy under direct endoscopic control. In 1853 the French surgeon Antonin Jean Desormeaux introduced his endoscope for the investigation of body cavities. The light of a flame was reflected into the body by a mirror. In 1865 he reported several cases in which he had incised urethral strictures under endoscopic vision with a thin knife passed down a lateral opening of the urethrotome sheath.⁶ Francis Richard Cruise from Dublin modified Desormeaux's instrument slightly and treated strictures by passing a Maisonneuve urethrotome down his endoscope.⁶ In 1877 Maximilian Nitze introduced his modern type endoscope with a platinum wire as an internal light source and an optical system in the shaft.⁶ Felix Martin Oberlander modified this system for the diagnosis and treatment of urethral disorders. Fenwick from London introduced an aero-urethroscope with illumination produced by an electric lamp at the lower end of the instrument being reflected into the urethral speculum by a mirror.⁶

Sachse combined effective optical illumination with cold knife urethrotomy to produce the urethrotome that is still most widely used in the world today.⁷ He reported retreatment rates as low as 23% and at the time his urethrotome was hailed as the solution to all urethral strictures. In reality the modern urethrotome does little different compared to the instrument as described by Maisonneuve, and not surprisingly later studies failed to achieve the excellent results reported by Sachse.

In the early 19th century there was some enthusiasm for external urethrotomy. In this open procedure the urethra is exposed and the stricture is laid open. A catheter is then passed from the meatus across the opened stricture and into the bladder. The peri-urethral tissues and skin are then closed over the catheter that stays in for several weeks. Guthrie described such a procedure in 1830 as did James Syme in 1844.

In 1883 Huesner performed an anastomotic urethroplasty. In 1906 Pasteau and Iselin described a two stage urethroplasty. In 1914 Hamilton Russell excised a stricture and anastomosed one wall of the remaining urethra, allowing the resulting defect to heal by secondary intention. He also described the two stage dorsal strip urethroplasty, verbalising a technique that was employed by and named after Dennis Browne years later.⁸

The perineal two-stage urethroplasty was described by Hamilton Steward in 1948 and Bengt Johanson in 1950.^{9,10} Swinney described a similar procedure in 1954.¹¹ From 1950 to 1970 the two-stage perineal urethroplasty as described by Johanson was the most commonly performed open operation for strictures of the bulbar urethra. During the first stage of the procedure the stricture is laid open via a perineal incision, and both a proximal and distal stoma are created. The second stage tubularisation is performed once the first stage has healed and the fibrosis has settled. Stenosis of both the proximal and distal meatuses created by the first stage procedure were common complications. Blandy addressed this by an inverted U-shaped incision, creating a generous scrotal skin flap to be sutured into the apex of the proximal urethrotomy.¹² Turner-Warwick modified this further by basing

his inlay flap on two lateral pedicles.¹³ Naude and De Kock used the same skin flap principle to prevent stenosis of the distal meatus.¹⁴

Strictures of the membranous urethra were traditionally treated by the pull-through operation as described by Badenoch.¹⁵ In this procedure the posterior urethra is mobilised and pulled in to the opened bladder on a catheter. This technique was previously described by Solovov in 1935 and Wells in 1941.¹⁶ Badenoch's technique was only applicable to very short strictures. To overcome this Waterhouse devised a modification whereby he performed a pubectomy, giving the surgeon direct access to the scarred area and shortening the route of the urethra being joined to the apex of the prostate.¹⁷ He employed this technique extensively in children with very proximal distraction injuries of the urethra.

Working independently, both Quartey in Ghana and Naudè in South Africa, adopted the dissection used in perineal prostatectomy to improve access to the apex of the prostate when dealing with membranous strictures. By opening the ischio-rectal fossae and then dividing the perineal body transversely, a plane is entered between the urethra and rectum, which can be followed all the way to the prostate.¹⁸

The search for a successful one stage urethroplasty for bulbar urethral strictures paved the way for pedicled skin flap and free graft urethroplasty. In 1963 Horton and Devine described a thin full-thickness penile skin graft used for hypospadias repair and subsequently as a ventral patch in a single stage bulbar urethroplasty.¹⁹ Penile skin is non hair bearing so this procedure did not share the hair related problems of scrotal flap procedures, but suffered a similar incidence of diverticulum formation. Turner-Warwick described "wet skin" and "dry skin".²⁰ "Wet" epidermal surfaces such as those of the urethra, the foreskin, the mouth and the vagina are adapted to their wet environment. "Dry" surfaces such as the scrotum or the thigh tend to become inflamed when constantly urine-sodden and as such are inappropriate for urethral reconstruction. Turner-Warwick described penile skin as semi-dry, hairless and moisture resistant.²⁰

In 1983 Quartey described the blood supply of the prepuce and penile skin.^{21,22,23} The bilateral superficial external pudendal arteries are branches of the first part of the femoral artery. These arteries cross the upper medial portion of the femoral triangle and divide into dorso-lateral and ventro-lateral branches that run within subcutaneous fascia of the penis. A pedicled-island flap based on this blood supply can reach any part of the urethra, right up to the apex of the prostate. Used as a patch or a tube, skin flap urethroplasty suffered the same complication of diverticulum formation as ventral free graft urethroplasty.

More recently Barbagli introduced the concept of placing a free graft in the dorsal aspect of a bulbar stricture. This innovation has proven to be a major advance in bulbar urethroplasty.^{24,25} The urethra is mobilised and opened dorsally without the need for urethral division. This is less likely to impair urethral blood supply. The graft is sutured to the inferior surface of the corporeal bodies providing an excellent graft bed and firm support thus preventing diverticular formation.

Attempts at endoscopic urethroplasty are not new. Nove-Josserand, 1919, quoted in Petterson et al reported a technique of hypospadias repair in which a skin graft was placed around a probe and introduced through a subcutaneous tunnel on the ventral aspect of the penis.²⁶ Petterson himself attempted endoscopic urethroplasty in the 1970's by tying split skin grafts to urethral catheters after optical urethrotomy.²⁶ This work was later repeated by Rosin and Edwards.²⁷ Naudè found skin grafts tied to Foley catheters unsuccessful, probably due to excessive movement between graft and graft bed.^{28, 29} Naudè developed a purpose specific graft carrying device and delivery system designed to keep the graft firmly secured and apposed to the graft bed. Naudè reported results comparable to that of open urethroplasty for the treatment of bulbar urethral strictures and membranous urethral injuries treated early after pelvic fracture.^{28, 29}

The most recent past has seen the development of off-the-shelf acellular matrix grafts for urinary tract reconstruction. This, together with the advances in cell culture techniques and tissue engineering, may prove to be a major breakthrough in reconstructive urology.

Current treatment of urethral strictures

Anatomical considerations

The blood supply to the penis is by three pairs of arteries that are all branches of the internal pudendal arteries. The arteries to the bulb supply the corpus spongiosum, urethra and glans of the penis. The deep arteries of the penis supply the corporeal bodies. The dorsal arteries of the penis supply the dorsal skin, fascia and provide some blood supply to the glans, thereby anastomosing with the supply from the arteries to the bulb. If the urethra is divided, as is inevitable with anastomotic urethroplasty, the blood supply to the distal urethral segment will depend on the somewhat tenuous retrograde flow from the dorsal arteries via the glans.

The bilateral superficial external pudendal arteries supply the penile skin and prepuce. These arteries are branches of the first part of the femoral artery. These arteries cross the upper medial portion of the femoral triangle and divide into dorso-lateral and ventro-lateral branches that run within the subcutaneous fascia of the penis.^{21, 22, 23}

The ventral aspect of the bulbar urethra is readily accessible via a perineal incision. Placing a graft or skin flap into a urethral stricture that has been opened ventrally is technically easy and has been performed for many years. The bulbar urethra has very little structural support on its ventral surface. In the case of a free graft the bulbocavernosus muscles have to provide the graft bed. Both grafts and flaps that are placed ventrally are prone to diverticulum formation due to the lack of structural support. On the contrary the dorsal aspect of the bulbar urethra is closely apposed to the corporeal bodies and thus very well supported. A dorsally placed graft enjoys an excellent blood

supply and structural support from the corporeal bodies and diverticulum formation is virtually impossible.

Principles of wound healing

The surgical treatment of urethral strictures is governed by the principles of wound healing. All wounds heal by a varying degree of wound contraction and repair, replacing lost tissue with granulation tissue and subsequent scar formation. Wounds are classically described to heal by either primary or secondary intention. The processes involved are basically the same, but differ in extent and relative importance. The degree of wound contraction and scar formation will depend on the size of any defect, the epithelial cover, and the dermal collagen content of any grafts covering a defect.

In the absence of any significant epithelial defect healing will be by primary intention characterised by minimal inflammation, wound contraction and scarring. In the event of a significant epithelial defect wound healing is by secondary intention, characterised by initial inflammation, marked wound contraction and subsequent scarring.

Granulation tissue formation consists of the three processes of inflammation, demolition and organisation. These three processes overlap. Inflammation is associated with an initial influx of inflammatory cells and stimulation of complement and leukotrienes. The influx of inflammatory cells is potentiated by increased vascular permeability and vasodilatation. Demolition of dead tissue is mediated by neutrophils and macrophages. The neutrophils predominate initially but macrophages play a very important role by secreting the chemical mediators necessary for normal wound healing. Wound healing cannot occur in the absence of macrophages. Macrophages and platelets secrete growth factors such as platelet derived growth factor and epidermal growth factor. These factors stimulate the migration and proliferation of fibroblasts that migrate into the fibrin mesh of the wound where they secrete collagen.³⁰ Organisation of the wound is characterised by initial vascularisation and subsequent maturation and devascularisation over time.

Wound contraction is mediated by myofibroblasts. The extent of wound contraction depends on the size of any epithelial defect and the dermal collagen content in the event of a graft such as skin or buccal mucosa applied to a graft bed. The presence of dermal collagen in a graft prevents wound contraction. Full thickness grafts of hairless skin or buccal mucosa are histologically similar, both containing a high dermal collagen content thus preventing wound contraction and scarring. Split skin grafts contain very little dermal collagen and not surprisingly are associated with marked wound contraction, fibrosis and scarring.

A wound or defect that is repaired by approximating two ends of vascularised, epithelialised normal healthy tissue that are free of tension will heal by primary intention. A spatulated, tension-free, anastomotic urethroplasty is an example of such a wound. If a defect or raw area is covered by vascularised epithelial tissue, or an epithelialised graft that takes well, then that wound will also heal by primary intention. This holds true, even if the introduced epithelialised tissue is different from the type of epithelium normally found in the organ where it is implanted. Examples of this latter scenario would be a stricture treated by means of a pedicled island flap of foreskin or a successful free graft of buccal mucosa.

A wound that is denuded of epithelium will heal by secondary intention. Healing by secondary intention is characterised by inflammation, wound contraction, and fibrosis. Simple cutting or dilatation of a stricture creates a large raw area denuded of epithelium that will tend to heal by secondary intention and subsequent scarring and stricture recurrence.

Endoscopic urethroplasty is based on the premise that an endoscopically placed graft can utilise the raw area created by optical urethrotomy as a graft bed, and provided that the graft takes, can ensure healing by primary intention with minimal wound contraction and scar tissue formation.

Dilatation and Optical urethrotomy

Blind dilatation and optical urethrotomy are both relatively easy to learn and quick to perform and do not require inpatient stay, general anaesthetic or operative theatre time. These procedures are effective in the short term but less so in the long term. Steenkamp et al compared dilatation with optical urethrotomy in a prospective randomised trial of 210 patients treated for urethral strictures and found the two treatment forms to be equally effective in the short term and equally ineffective in the long-term maintenance of urethral patency.^{31,32} There was no statistical difference between the two treatments with regards to long term stricture recurrence. The recurrence rate at 12 months was 40% for strictures shorter than 2cm and 80% for strictures longer than 4cm. Heyns et al re-evaluated the data from this trial with a view to ascertain whether repeated dilatation or urethrotomy is of any value in the long-term maintenance of urethral patency. He found that dilatation or internal urethrotomy is useful in about 70% of patients who will be stricture free at three months and of whom 50 to 60% will remain stricture free at 48 months. A second dilatation or urethrotomy at three months is of limited value in the short term but of no value in the long term with a recurrence rate of 100% at 48 months. A third repeated dilatation or urethrotomy is of no value.³³ A second dilatation or urethrotomy that is performed for a stricture recurrence occurring long after the initial procedure may be of long-term benefit in some patients.

Pansadoro and Emiliozzi evaluated the long term results of 224 patients who underwent optical urethrotomy and were followed up for at least five years.³⁴ They reported a recurrence rate of 58% for bulbar urethral strictures treated by optical urethrotomy. In patients with strictures shorter than 1cm the recurrence rate was only 29%. Repeat urethrotomy in patients with recurrent bulbar strictures provided short-term relief but ultimately failed in 100% of patients.

Dilatation or optical urethrotomy are both such simple procedures that most patients with short uncomplicated bulbar strictures deserve a trial of one or

perhaps two of these treatments. Longer strictures or strictures associated with marked spongiofibrosis are likely to fail treatment with dilatation or optical urethrotomy. Some authors have raised the concern that failed urethrotomy may magnify the extent or length of an existing stricture and might adversely affect the outcome of a subsequent repair. This has however never been proven. Barbagli et al compared the outcomes of patients that underwent primary urethroplasty with similar patients who underwent urethroplasty after previous failed urethrotomy. They reported no difference in outcome.³⁵

Intermittent self dilatation

Some patients are not suited for major urethroplasty surgery, either due to their age, co-morbid disease, or patient choice. Urethral patency can be maintained very effectively in most patients by means of intermittent self dilatation. Self-dilatation with a standard round tipped catheter is successful if performed frequently. However as soon as the stricture narrows to less than the diameter of the catheter it will not navigate the stricture and a clinic dilatation or optical urethrotomy will usually be needed. The shearing longitudinal force created by a round tipped catheter that is larger than the diameter of the urethra is considerable. Conversely the dilating force is minimal in such a situation.

Naude developed an integrated filiform / follower with a very gradually tapered shoulder for self dilatation after optical urethrotomy. This dilator / follower is manufactured by Cook. The filiform tip ensures that even fairly tight strictures can be negotiated. The very gradual taper of the shouldered segment ensures a large dilating force at a right angle to the surface of the dilator.

Figure 2 - Principles of wedge mechanics

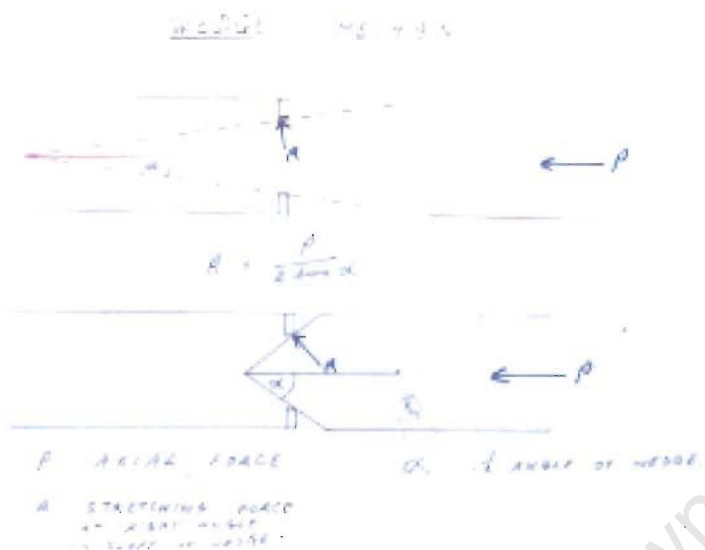
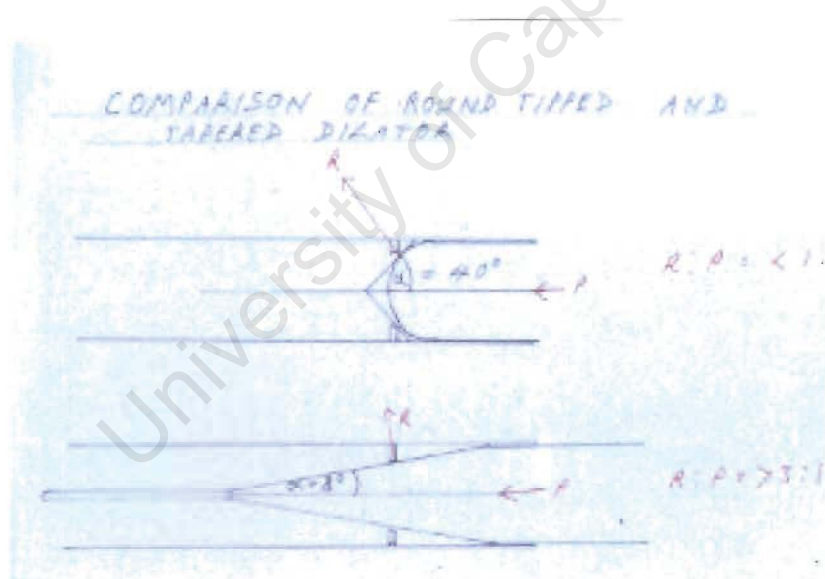


Figure 3 - Round tipped versus tapered dilator



The proposed protocol following optical urethrotomy is as follows: The catheter is left indwelling for a week after the optical urethrotomy, as immediate self dilatation might result in false passage formation. For the subsequent three weeks daily self catheterisation with a round tipped catheter is performed. Thereafter intermittent self dilatation with the filiform tipped dilator is initiated three times per week, gradually increasing the interval to

reach a monthly dilatation at six months. This is then maintained in the long term. If the passage of the dilator is at all difficult, the interval between dilatations is halved.

Anastomotic urethroplasty

Open urethroplasty refers to the open surgical repair of a stricture. In the case of a membranous stricture following a pelvic fracture the standard treatment is an anastomotic urethroplasty performed via a perineal approach three to six months after a period of suprapubic bladder drainage. A surgeon skilled in this procedure can almost always anastomose the bulbar urethra to the apex of the prostate, irrespective of the length of the distraction defect between the two urethral ends. The long-term success rates are quoted at more than 90% but these patients do have the considerable inconvenience of prolonged suprapubic catheter drainage.^{36,37,38} Due to long waiting lists the period of suprapubic drainage can exceed six months. During this time the patient's participation in work, sport, as well as social and sexual activity can be severely curtailed.

Short bulbar urethral strictures are also best treated with excision of the strictured area and an anastomotic urethroplasty if possible. The aims of the procedure are to achieve a tension-free, spatulated anastomosis. Success rates as high as 95% are quoted.^{39,40} Unfortunately anastomotic urethroplasty is only suitable for strictures up to 2cm in length. Various manoeuvres can be performed to create urethral length in an effort to provide a tension-free anastomosis. These manoeuvres are all aimed at eliminating the natural curve in the course of the bulbar urethra to provide a more direct route between the two urethral ends. These include, in sequence: adequate urethral mobilisation, splitting of the corporeal bodies in the midline, inferior pubectomy, and rerouting of the urethra around one of the corporeal bodies.^{37,41,42} Attempting to treat longer bulbar strictures with anastomotic urethroplasty can cause tension on the anastomosis leading to breakdown. Even if the anastomosis is successful inadequate urethral length will cause chordee with erections.

Substitution urethroplasty

Bulbar urethral strictures longer than 2 cm are not suitable for anastomotic urethroplasty. Some form of free graft or vascularised pedicled flap from outside of the urethra is needed to fill the defect or bridge the gap between the proximal and distal normal urethral ends. Both grafts and flaps can be used either as patches or as tubes, depending on whether circumferential urethral replacement is needed or not. If a strip of urethra can be preserved then a graft or a flap can be used as a patch to fill the defect. If this is not possible and a circumferential segment of urethra needs to be replaced then the graft or flap needs to be tubularised. In general both grafts and flaps are more effective when used as patches rather than as tubes. Occasionally the divided urethral ends can be spatulated on ipsilateral sides and the tongues of the spatulated ends can be anastomosed leaving a diamond shaped defect in the roof of the urethra to be filled by a patch of a vascularised pedicled flap or a free graft. This is the so-called augmented roof strip urethroplasty.

Skin flap urethroplasty

By definition skin flaps are areas of skin that are mobilised on an intact blood supply and transposed to where they are needed. Currently the most commonly used flaps are pedicled island flaps of prepuce or distal penile skin mobilised on the pedicle running in the subcutaneous tissues of the penis. Quartey described the blood supply of the prepuce and penile skin.^{21,22,23} The bilateral superficial external pudendal arteries are branches of the first part of the femoral artery. These arteries cross the upper medial portion of the femoral triangle and divide into dorso-lateral and ventro-lateral branches that run within the subcutaneous fascia of the penis. In those patients who had previously had a circumcision the distal penile skin proximal to the corona of the glans can be used in the same way as the foreskin in those who have not been circumcised. A mobilised island of foreskin or distal penile skin can reach any part of the male urethra, right up to as high as the membranous urethra. The island of skin can be used as a patch if a stricture can be cut open and the urethral plate preserved, or as a tube if circumferential urethral replacement is required.

Many of the earlier urethroplasty procedures incorporated scrotal skin into the newly formed urethra due to its abundance and close proximity. The use of scrotal skin was associated with a high incidence of complications and has now largely been abandoned in favour of preputial and penile skin grafts or free flaps of buccal mucosa or hairless skin. Scrotal skin is not well suited to the wet environment of the inside of the urethra. It is thermolabile and thus difficult to size accurately, often leading to diverticular formation later on. The hair on scrotal skin causes encrustation that can be difficult to manage.

In a paper recording the retrospective 10 year follow up of 73 patients who had undergone skin-inlay urethroplasty, Mundy reported superior results using preputial or penile skin flaps as compared to scrotal skin flaps.⁴³ Flaps used as a patch fared better than those used as a tube. The perceived wisdom has always been that most strictures recurring after urethroplasty will do so in the first 12 months following the procedure. Mundy clearly showed that there is a steady attrition over time for skin inlay urethroplasty. The re-stricture rates for all skin inlay urethroplasties utilising a patch were 19% at five years and 40% at 10 years. When the skin flap was used as a tube the re-stricture rates were 36% at five years and 56% at 10 years. Tubularised scrotal skin flaps fared worst of all with a re-stricture rate of 89% at 10 years. McAninch reported very good results with a circular fasciocutaneous penile flap based upon Buck's fascia vascularisation.⁴⁴ In 40 patients with urethral strictures up to a maximum length of 15 cm he reported an overall success rate of 85%. Some authors reported very good results with scrotal skin flaps but in general these results were not reproducible.^{39,45}

Although most instances of stricture recurrence after urethroplasty will occur during the first 12 months, Mundy clearly demonstrated that there is significant long term attrition over time with skin flap urethroplasty.⁴³ Successful preputial and distal penile skin flap urethroplasty can also cause some cosmetic changes which can be bothersome. There will be scarring from the area where the flap was taken. Some degree of rotation of the penis is almost inevitable since the pedicle of the flap has to course around the shaft of the penis unless the pedicle has been buttonholed with the penis

passing through the buttonhole in the pedicle. The pedicle can also cause unsightly webbing of the penis.

Free graft urethroplasty

Free grafts are transplanted without any intact blood supply. Free grafts need to survive by the process of imbibition of nutrients for 24 to 48 hours until inosculation occurs, by which time new capillaries have entered the lamina propria of the graft. This process of graft take generally takes four days.⁴⁶

Split thickness skin grafts take well because they are thin and possess a well developed intradermal vascular plexus. Unfortunately split skin grafts undergo marked fibrosis and contraction due to a lack of dermal collagen after implantation and are not suitable for one stage urethral reconstruction. Full thickness skin grafts on the other hand rely on the subdermal plexus for graft take. Full thickness grafts generally take less well than split skin grafts. Once they do take they contract much less than split grafts due to the high dermal collagen content.

The most commonly used full thickness free grafts are buccal mucosa and hairless full thickness skin. Buccal mucosa consists of non-keratinised stratified squamous epithelium. It is histologically similar to hairless skin found above the jaw line, and differs from the latter only in regard to keratinisation. It is suited to the wet environment of the urethra and is extremely resistant to infection. Preputial skin, distal penile shaft skin, hairless skin from above the jaw line and buccal mucosa all share the characteristic of a very well developed subdermal plexus, ensuring good graft take. Hairless skin is only found on the prepuce and penile shaft and above the jaw line on the face. Due to obvious aesthetic reasons the only realistic extra-genital sources of hairless skin are the retro-auricular areas. These retroauricular grafts are also called Wolfe grafts.

The ideal free graft should be:

- plentiful

- easy to harvest

- donor site should heal well without any complications

- handle well
- take well in the urethra
- undergo minimal contraction or stretching after implantation
- suited to the wet urethral environment

The ideal free graft does not exist. Full-thickness buccal mucosa is probably the best currently available biological free graft. It meets most of the above criteria for the ideal graft. Buccal mucosa can be harvested from the inside of one or both cheeks, as well as from the inside of the lower lip. At our institution the inside of the cheek is the preferred site. The harvesting itself is easy to perform and the donor site generally heals quickly and without complications. There is an adequate amount of buccal mucosa available even for extensive urethral reconstruction. Buccal mucosa has a thin submucosa and a well developed subdermal plexus ensuring good graft take. The non-keratinised stratified squamous epithelium is well suited to the wet environment of the urethra. These are full thickness grafts with a high dermal collagen content ensuring minimal graft contraction after implantation. Harvesting buccal mucosa does however take a certain amount of time and the patient ends up with two operative wound sites. Although the mouth heals well in the vast majority of cases there obviously is some discomfort and pain from the harvest site.

Dorsal or ventral patch graft urethroplasty?

Traditionally the standard free graft patch urethroplasty for bulbar urethral strictures involved a ventral urethrotomy through the stricture with a free graft sutured into the defect over a urethral catheter. This procedure did not always provide a reliable graft bed and provided very little structural support for the graft. Stretching of the graft over time with diverticulum formation is a common complication affecting ventrally placed grafts.

Barbagli has introduced a brilliant and innovative approach to bulbar urethroplasty.^{24,25} By placing his free grafts of full-thickness penile skin or buccal mucosa dorsally, he at once overcame several of the earlier problems with free graft urethroplasty. There are many obvious advantages in placing

the graft dorsally. The urethra is mobilised and opened dorsally without the need for urethral division. This is less likely to impair urethral blood supply. The graft is sutured to the inferior surface of the corporeal bodies providing an excellent graft bed and firm support thus preventing diverticulum formation.

In 1998 Barbagli et al published the results of the dorsal onlay patch urethroplasty in 37 patients. They used full thickness penile skin in 31 of these cases and buccal mucosa in six. Any patient who needed any subsequent procedure was deemed a treatment failure. With a mean follow up of 21.5 months (range 7 to 47 months) the overall success rate was 92%.²⁴ Iselin and Webster reported promising early results using this technique with dorsally applied penile skin grafts in 27 patients.⁴⁷

Figure 4 - Dorsal buccal patch urethroplasty as described by Barbagli



Pansadora and Emiliozzi used free buccal grafts in 65 patients with bulbar strictures. The minimum follow up was 37 months. One (11%) of nine patients who underwent ventral graft placement developed stricture recurrence, whereas there were no cases of stricture recurrence in 56 patients in whom the grafts were applied dorsally.⁴⁸ In 2001 Andrich and Mundy reported a series of 128 patients treated with buccal graft urethroplasty. 117 Of these patients underwent patch graft urethroplasty. With a minimum follow up of two years the re-stricture rate was 11%. In 11 patients in whom the buccal grafts were used as tubes for circumferential urethral replacement the re-stricture rate was 45%.⁴⁹

Skin flaps or free grafts?

Full-thickness penile skin grafts were pioneered by Horton and Devine in 1963 but fell somewhat out of favour.¹⁹ The scrotal flap enjoyed similar transient popularity, but were superseded by pedicled island skin flaps of prepuce or distal penile skin.^{21,22,50} The excellent results reported with the use of buccal mucosa, especially as a dorsal patch as described by Barbagli, has led to a shift back in favour of free graft urethroplasty. So much so that the dorsal patch urethroplasty with a free graft of buccal mucosa for those bulbar strictures not suited to anastomotic urethroplasty has become the procedure of choice of many leading reconstructive urologists. As recently as 1995 Mundy stated that "the present author's bias is strongly in favour of pedicled skin flaps as against free grafts".⁴³ The same author is now using free buccal grafts extensively.

Wessels and McAninch reviewed the literature on free-graft and pedicled skin flap urethroplasty in an attempt to determine the optimal repair. Overall they found free grafts to be successful in 84.3% of cases and pedicled flaps in 85.9% of cases.⁵¹ This statistic includes both bulbar and penile urethroplasty. They report buccal mucosa free graft urethroplasty to be the most successful method in bulbar urethral strictures not suitable for anastomotic repair. Free grafts are generally easy to harvest. Free graft urethroplasty is probably technically slightly easier and quicker to perform than skin flap urethroplasty. The cosmetic result with a free graft of buccal mucosa is superior to that of a pedicled skin flap urethroplasty. In the event of an unreliable graft bed as would be encountered with sepsis or marked fibrosis, Wessels and McAninch favour a pedicled island flap urethroplasty because of its reliable blood supply.⁵¹ In very complex cases that also involve the pendulous urethra Mundy is reverting to two stage procedures, often using buccal mucosa as a graft in the first stage.⁵² Tubularised free grafts consistently fare worse than patch free grafts. Tubularised skin flaps also fare much worse than skin flaps that are applied as patches.

Endoscopic tissue graft urethroplasty

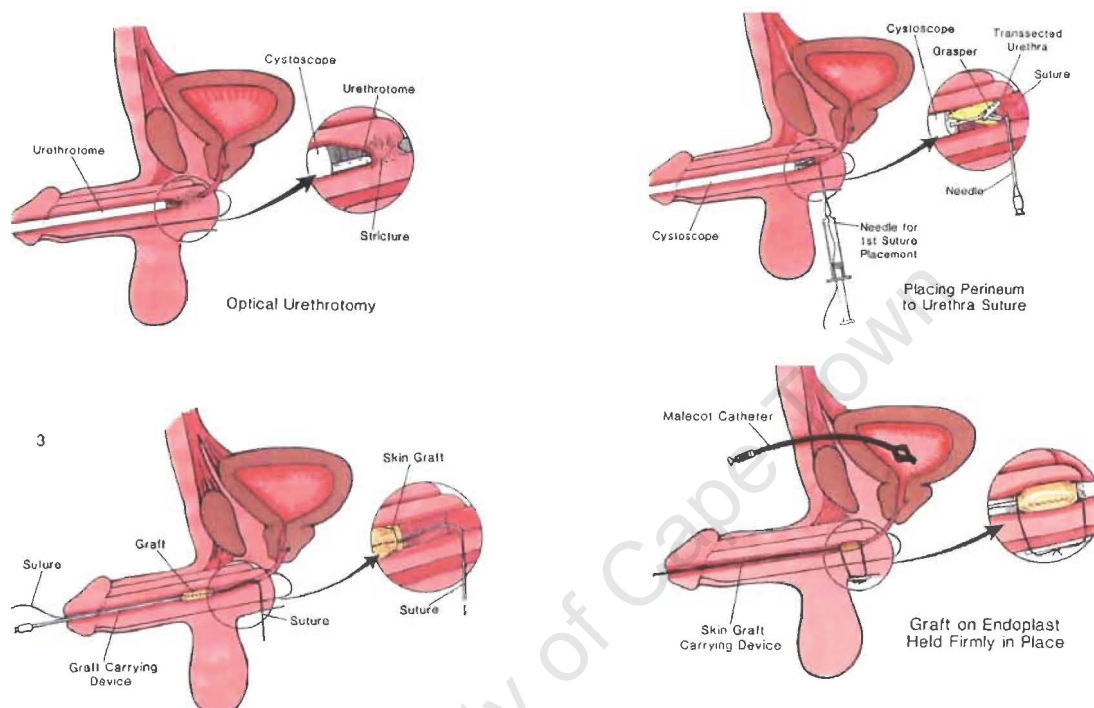
Endoscopic urethroplasty involves the endoscopic placement of a graft into the area of a urethral stricture after the stricture has been cut open by an optical urethrotomy. This is not a novel idea. Endoscopic urethroplasty is based on the following concept: Generous optical urethrotomy of a bulbar urethral stricture into normal surrounding tissue creates a large raw area that will act as a graft bed. If a graft can be placed in the opened urethra and kept in place without undue movement between graft and graft bed then the graft will take in areas where it is in contact with graft bed and merely undergo necrosis in areas in contact with normal urethral epithelium. A defect covered by an epithelialised graft heals with primary intention and minimal or no fibrosis, whereas an uncovered defect heals by secondary intention characterised by fibrosis and wound contraction.

Petterson et al attempted endoscopic urethroplasty in the 1970's by tying split skin grafts to urethral catheters after optical urethrotomy.²⁶ This work was later repeated by Rosin and Edwards.²⁷ In 1983 Gaur published a series of seven cases of endoscopic urethroplasty also incorporating split skin grafts tied to Foley catheters.⁵³ He modified a standard Foley catheter by placing a balloon inside the main lumen of the Foley catheter in the area where the graft is to be applied. By inflating this intraluminal balloon he distended the Foley catheter slightly in an attempt to ensure close apposition of the graft to the graft bed. This appears to be one of the first attempts at a purpose specific balloon graft carrying device, but his technique never became widely accepted. Naudè found skin grafts tied to Foley catheters unsuccessful, probably due to excessive movement between graft and graft bed.^{28,29}

Naudè developed a purpose specific graft carrying device and delivery system designed to keep the graft firmly secured and apposed to the graft bed. The endoplast graft carrying device is manufactured by Cook. The procedure is fully described in a later section of this work. Two sutures that are attached to the proximal and distal ends of the device and are tied on the perineum prevent any longitudinal movement of the graft carrying device. The balloon

is inflated to a predetermined volume and ensures close apposition between the graft and the graft bed.

Figure 5 - Steps in endoscopic urethroplasty



Naudè reported the results of 53 patients treated by endoscopic urethroplasty using full thickness hairless skin grafts, and followed up for at least two years.²⁹ Failure was defined as the need for any further intervention. In 25 patients with inflammatory and iatrogenic strictures the graft take rate was 95% and all of these patients maintained long term urethral patency. In 10 patients treated soon (2 – 3 weeks) after pelvic fracture with urethral rupture the graft take rate was 100%. Two of these patients were lost to follow up and two required subsequent optical urethrotomy. Six patients maintained long term patency without any intervention.²⁹

In 16 patients with established strictures following pelvic fracture the results were not good. Graft take was 80% and in 50% of these patients the

strictures recurred, giving an overall success rate of 40%. Naudè's experience with endoscopic skin graft urethroplasty in patients with established strictures following pelvic fracture is contrary to that of Chiou.⁵⁴ Chiou reported successful endoscopic urethroplasty in three patients with established strictures associated with marked fibrosis. In two of these patients the strictures were secondary to pelvic fractures years before. He described a two-stage endoscopic urethroplasty. During the first stage he resected the fibrotic scar tissue to create a graft bed. After three to four days he scraped the resultant granulation tissue to create a raw area. A full thickness skin graft applied to a graft carrying device was then applied to this graft bed. Two of Chiou's three patients underwent optical urethrotomy within the first year after the initial endoscopic urethroplasty.⁵⁴

Oosterlinck and Talja applied full thickness penile skin grafts to a biodegradable polyglycolic acid spiral stent that they secured in the urethra by means of a suture passed from the perineum. They applied this technique in 10 patients with bulbar urethral strictures of 2 – 4 cm in length that have failed optical urethrotomy and would have qualified for open urethroplasty. At a mean follow up of 21 months (range 3 – 39 months) they reported only one stricture recurrence.⁵⁵ In our experience polyglycolic acid stents used without skin grafts were unsuccessful in maintaining urethral patency following optical urethrotomy. The stents inserted at our institution all caused exuberant ingrowth of urethral epithelium causing urethral narrowing. This study was terminated after only 5 cases due to obvious bad results.⁵⁶

Naude's results of endoscopic urethroplasty are comparable to conventional open urethroplasty in those patients with inflammatory or iatrogenic strictures and in patients with distraction injuries of the urethra treated early (2-3 weeks) after pelvic fracture.²⁹ Endoscopic urethroplasty has many obvious advantages over open urethroplasty. It is a minimally invasive technique that is quick to perform and easy to learn. It does not share the complications of open urethroplasty associated with the perineal wound incision or the mobilisation of penile skin flaps. It is very unlikely to interfere with erectile function. The hospital stay and post-operative recovery is short. Patients can

go home during the first 24 hours after the procedure. During this initial period free grafts survive by imbibition and absolute immobilisation is not essential. Patients should then remain on bedrest at home for four days during the period of graft take. Patients can return to full physical activity within two weeks. In the event of a treatment failure a virginal operative field remains for an open urethroplasty. The patient is no worse off than if he had a failed optical urethrotomy.

One of the few disadvantages of endoscopic urethroplasty is the need for obtaining a skin graft. This adds to the operative time of the procedure. The harvest site is also associated with discomfort and scarring. If this procedure could be performed successfully with a manufactured biological graft it would be even more attractive. An effective "off the shelf" graft would obviate the need for graft harvest from the patient. This would markedly reduce operative time and patient morbidity.

In the North American literature the term endoscopic urethroplasty is sometimes used to refer to the endoscopic realignment of the posterior urethra following urethral rupture associated with pelvic fracture. There are several published series containing small numbers of patients that describe these methods of managing membranous urethral rupture several months after the injury.^{57,58,59}

Continuity is established between the bladder and urethra by endoscopic resection of the scar tissue, often combining a retrograde and antegrade approach. A catheter is left in situ for several weeks in the hope that the channel will epithelialise with urothelium. While it may often be possible to create a channel between the urethra and bladder in this manner, few of these patients maintain urethral patency without intermittent dilatation or optical urethrotomy. We favour an anastomotic urethroplasty for patients with urethral injuries treated long after pelvic fracture, or skin graft endoscopic urethroplasty for those that can be treated early (two to three weeks) after pelvic fracture. In this dissertation endoscopic urethroplasty refers to endoscopic tissue graft urethroplasty.

Current practice at our institution

The current treatment policy for urethral strictures managed at our institution is as follows: Short simple strictures in an otherwise healthy urethra are treated by optical urethrotomy once. Recurrence qualifies the patient for urethroplasty, unless the recurrence is years after the original urethrotomy in which case a second optical urethrotomy may be of benefit. Penile urethral strictures are treated by pedicled island flap urethroplasty using foreskin or distal penile shaft skin when foreskin is not available. Very short bulbar strictures such as those caused by fall-astride injuries are treated by spatulated anastomotic urethroplasty. Longer bulbar strictures are treated by dorsal onlay urethroplasty of buccal mucosa or penile skin as described by Barbagli, or by endoscopic tissue graft urethroplasty with the use of penile skin. Membranous strictures and distraction injuries presenting late are treated by anastomotic urethroplasty. Recent rupture of the urethra associated with pelvic fracture is treated with endoscopic tissue graft urethroplasty two to three weeks after the pelvic fracture. Optical urethrotomy or clinic dilatation, followed by intermittent dilatation, is used to treat the frail and elderly. In those patients in who repeated dilatation will be required self dilatation is instituted whenever possible. We prefer a filiform tipped tapered dilator designed by Naudè for this purpose.¹

SurgiSIS

SurgiSIS or SIS is an acellular, non-immunogenic, biodegradable, collagen matrix graft manufactured from porcine small intestinal submucosa. At the time of our study surgiSIS had been extensively tested in laboratory animals and had been granted FDA approval for use in human trials. It has subsequently been granted full FDA approval for urinary tract reconstruction. Similar biological acellular collagen matrix grafts are manufactured from bladder submucosa (BAMG) and cell free dermis.⁶⁰

Small intestinal submucosa (SIS) is manufactured from porcine small intestinal submucosa. We used surgiSIS that is manufactured by Cook. The manufacturing process involved to prepare the grafts is briefly as follows:

Sections of porcine small intestinal mucosa are harvested immediately after euthanasia. The mesentery is removed. The tunica mucosa is mechanically removed from the inner surface and the serosa and tunica muscularis are removed from the outer surface. This produces a thin, translucent graft (0.1 – 0.2mm wall thickness) consisting of the stratum compactum and muscularis mucosa of the tunica mucosa with the attached submucosa. The graft consists of a thin, acellular, collagen-rich matrix. SurgiSIS is sterilised with ethylene oxide, freeze-dried and packaged. It is soaked in saline for 10 minutes prior to use. It is surprisingly strong and handles well.

Surgical reconstruction of the urinary tract is hampered by the lack of available native urothelium. Despite all the well-known complications of placing bowel segments in the urinary tract this still forms the mainstay of reconstruction of the bladder and ureters. Urethral reconstruction is usually performed either by a genital skin flap or by a free graft of skin, buccal mucosa or perhaps bladder mucosa. None of these methods of urethral reconstruction are ideal or free of complications. Adult epithelialised tissue heals by varying degrees of scarring. During the foetal period human tissue has the ability to replace damaged or lost tissue with the regeneration of new normal tissue. During the first two trimesters skin lesions in a human foetus will heal by regeneration of all skin components, rather than by scarring.

Tissue engineering is a rather loosely used term that refers to techniques aimed at regenerating autologous, viable tissues. These techniques can be subdivided into two groups. In in-vitro tissue engineering autologous cells are cultured outside the body and later returned as autotransplants, either as coherent tissue structures or as cell suspensions. In-vivo tissue engineering involves methods aimed at stimulating the regeneration of native tissue by implanting materials or substances that regulate cell function and guide tissue regeneration. The use of unseeded collagen matrix grafts such as SIS is an example of in-vivo tissue engineering.

Unseeded acellular collagen matrix grafts such as SIS provide a scaffold for the regeneration and regrowth of the host organ or tissues. These grafts do

not function in the same way as implants of viable grafts of skin or buccal mucosa. The grafts do not have to survive by initial imbibition of oxygen and nutrients and there are no cells present that will undergo necrosis. Instead these grafts rely on the native angiogenesis of the host tissue to promote regeneration. Angiogenesis is present in implanted matrix grafts after three days. The grafted area rapidly becomes epithelialised and vascularised, and healing is by regeneration rather than by scar tissue formation.

SIS was initially tested as a vascular graft material in the dog. It functioned well as a venous or arterial graft with rapid replacement by native tissues^{61,62,63} However, the grafts did not only function well as vascular grafts, but became remodelled and replaced by the host and eventually impossible to differentiate from the native arterial or venous tissue. SIS grafts have also been used to replace knee ligaments and Achilles tendons in canine experiments. Within weeks fully developed ligaments and tendon tissues were present.⁶⁴

Kropp et al demonstrated successful bladder regeneration using unseeded SIS for bladder augmentation, first in rats and then in dogs. They performed partial cystectomy with immediate bladder augmentation with unseeded SIS grafts in 22 Sprague-Dawley rats.⁶⁵ Bladders were harvested at 2, 4, 8, 24 and 48 weeks. At two weeks the SIS grafts were completely covered by transitional epithelium. The grafts showed prominent neovascularisation at the graft edges and infiltration of the entire graft surfaces with fibroblasts and new capillaries. A moderately intense mononuclear inflammatory response was noted at the periphery of the grafts, with less intense inflammation in the centre of the grafts. By four weeks the grafts were completely infiltrated by well-formed small blood vessels and fibroblasts. Smooth muscle cells were present at the periphery of the grafts at this stage. At three months inflammatory activity had subsided and small well-formed blood vessels persisted. Collagen was well organized and distinct bundles of smooth muscle cells were present. At 24 and 48 weeks after augmentation all three layers of normal rat bladder were present in normal orientation and grossly and microscopically indistinguishable from normal rat bladder. There was no

evidence of graft shrinkage. Some of the animals had formed hydroxyapatite bladder calculi.

A polymorphonuclear cell inflammatory response was minimal or absent at all times during the study on rat bladder augmentation. The histological findings suggest a fibrovascular healing reaction. Smooth muscle cells also appear to have a regenerative capacity. Smooth muscle cells were sparsely present at four weeks and fully organised and indistinguishable from normal bladder at 11 weeks. It is not clear whether the smooth muscle cells represent ingrowth of native detrusor from the graft edges or production of detrusor smooth muscle cells from pericytes accompanying the capillary endothelial cells.^{65,66} Wefer et al reported similar findings using a bladder acellular collagen matrix graft in augmentation cystoplasty in rats.⁶⁷

Kropp et al performed partial cystectomy with immediate SIS graft bladder augmentation in 13 dogs.⁶⁸ In the control arm of the study partial cystectomy and primary bladder closure were performed. The dogs were sacrificed at various intervals up to 15 months. They evaluated serum biochemistry, bladder urodynamic assessment and histopathological findings in the SIS regenerated bladder segments. Serum biochemistry evaluation was normal for all dogs at all times during the study. The SIS regenerated bladders demonstrated stable capacity and normal bladder pressures throughout the study. Histologically the SIS regenerated bladder segments resembled normal canine bladders. The bladders that were harvested at one month demonstrated a mild mononuclear infiltrate. This was absent in bladders harvested at a later stage. At all time points examined all three layers of the bladder were present, consisting of mucosa covered by transitional epithelium, smooth muscle, and serosa, orientated in the normal fashion. The organisation of the smooth muscle layer was haphazard in some regions of the SIS regenerated bladder segments. There was no evidence of anastomotic scar formation or a suture line in any of the SIS-regenerated bladder segments. There was no microscopic evidence of any residual graft material in any of the bladders examined.⁶⁸

Kropp et al went on to assess the reinnervation, in vitro compliance and contractility on SIS regenerated canine bladders. Compliance studies demonstrated no significant difference between SIS regenerated and control bladders. The SIS regenerated bladders were 30 times more compliant than the unused SIS graft material itself. Contractility studies demonstrated contractile responses and innervation similar to those of native canine bladders. Afferent nerves were demonstrated within the regenerated bladder segments by immunohistochemistry techniques.⁶⁹

The two studies by Kropp demonstrated that SIS grafts can be safely implanted into canine bladders without evidence of graft rejection, graft shrinkage or systemic bladder related complications. The histological findings indicate a regenerative healing process rather than scar tissue formation. This rapid regenerative healing process with a distinct lack of scar tissue formation is similar to the scar free healing observed in fetuses.⁶⁸ SIS has never been shown to cause host immunogenic responses in cross-species transplantation.^{70, 71}

We used unseeded surgiSIS in our study. Most of the more recent research in the use of matrix grafts such as SIS has focused on cell-seeded grafts. Tissue culture facilities are needed to produce cell-seeded grafts. A biopsy is taken from the intended host and using cell culture techniques epithelial and smooth muscle cells are harvested and expanded in vitro. These cells are then seeded on to a graft such as SIS, and a composite graft is thus created in vitro prior to implantation. A large regenerated composite graft can be created within five weeks of a cold-cup bladder biopsy taken for cell culture.

Atala performed bladder augmentation in dogs using a collagen matrix graft obtained from bladder submucosa.⁷² Partial cystectomies were performed in dogs. Urothelial and smooth muscle cells were harvested and expanded separately in vitro. In one arm of the study the matrix grafts were seeded with urothelial cells on one side and smooth muscle cells on the other.

Augmentation cystoplasty was performed with seeded matrix grafts in one arm and unseeded matrix grafts in the other. The bladders augmented with

the cell-seeded grafts showed a 99% increase in bladder capacity and good function. The bladders augmented with unseeded matrix grafts showed only a 30% increase in capacity, as well as graft contraction and shrinkage.⁷²

Liatsikos et al used small intestinal submucosa grafts in partial upper ureteric replacement in the porcine model.⁷³ Six pigs had two thirds of the left upper ureter replaced with SIS grafts over a stent. On the right hand side an intubated Davis ureterotomy was performed and this acted as the control arm of the study. All animals survived the seven week follow up. Retrograde pyelography confirmed patency in all the ureters that were bridged with SIS grafts. All the right sided ureters treated without SIS grafts had undergone stenosis.⁷³

Several studies have demonstrated the successful regeneration of the urethra in experimental animals when using unseeded SIS or other similar collagen matrix grafts in an onlay fashion in open urethroplasty. Kropp et al compared unseeded SIS with preputial skin as onlay grafts in rabbit urethras. They found that unseeded SIS promoted urethral regeneration in all cases without any stricture formation, and reported SIS to be superior to preputial skin in this application.⁷⁴ The SIS regenerated urethras demonstrated normal rabbit urethral epithelium supported by a well-vascularised collagen and smooth muscle backing. Grossklaus successfully used SIS as a covering layer after ventral urethrotomy in rabbit urethras.⁷⁵

Chen implanted unseeded collagen matrix grafts manufactured from porcine bladder submucosa into defects created in the ventral aspect of 10 male rabbit urethras.⁷⁶ All the animals survived until being sacrificed without any voiding dysfunction. Serial urethrograms demonstrated patent urethras in all the animals with up to six months of follow up. Histologically the implanted matrices contained host cell infiltration and angiogenesis two weeks after surgery. Unorganised muscle bundle fibres were present at two months after implantation, and organised muscle fibres were present at six months after surgery.⁷⁶

Unseeded SIS has proven to be less successful in circumferential urethral replacement. De Filippo et al compared matrix grafts seeded with smooth muscle cells with unseeded matrix grafts in circumferential urethral replacement in rabbits.⁷⁷ In the group treated with unseeded grafts they encountered strictures with fibrosis in all cases. In all of cases treated with cell-seeded grafts they reported widely patent urethras without any fibrosis. Histologically the regenerated urethral tissue appeared normal with organised transitional epithelial and smooth muscle layers.⁷⁷ These results were published after we had conducted our study.

At the time our study was performed pioneers such as Atala had started to use acellular matrix grafts in open urethroplasty in human patients.⁷⁸ He used a bladder collagen matrix graft obtained from cadaveric bladders in four patients with a history of failed hypospadias surgery and a resultant absence of penile skin for reconstruction. The matrix grafts were used in an onlay fashion to reconstruct neourethral segments ranging from 5 to 15 centimetres. Three of the four patients had a satisfactory outcome. One patient who underwent a 15 cm urethral reconstruction developed an urethrocutaneous fistula.⁷⁸

O'Connor published the first ever case report using an unseeded SIS graft to successfully repair an uretero-neobladder stricture that had previously failed endoscopic treatment. Despite severe scar tissue and fibrosis repair with a tubularised SIS graft was successful.⁷⁹ Knoll used SIS grafts for the closure of the tunica albuginea after plaque incision for Peyronie's disease. He achieved correction of the penile curvature in 11 out of 12 patients.⁸⁰ Knoll also used SIS grafts to repair tunica albuginea defects caused by erosion of penile prostheses. He achieved closure of the tunica in all of 17 patients without removing any of the prostheses.⁸¹

Endoscopic urethroplasty with SurgiSIS collagen matrix grafts – a pilot study

Purpose of the study

The purpose of the study is to evaluate SurgiSIS as a substitute for skin in endoscopic urethroplasty performed as treatment for inflammatory and iatrogenic strictures of the male bulbar urethra and in the early treatment of bulbomembranous urethral injuries associated with recent pelvic fractures. The tissue integration and epithelialisation of SurgiSIS used in endoscopic urethroplasty is assessed. The long term maintenance of urethral patency following this treatment form is assessed.

Patients

Initially it was proposed that 10 male patients with bulbar urethral strictures be treated with the procedure of endoscopic urethroplasty using SurgiSIS grafts instead of skin. Nine patients were enrolled and operated on during the period from 15 July 1999 to 27 June 2000. We terminated enrollment after 9 patients when it became patently obvious that the procedure was not successful. The strictures were defined by pre-operative urethrography in all cases. Informed consent was obtained from all patients. 7 patients had presumed inflammatory strictures and 2 had suffered recent pelvic fracture with urethral injury.

Table 1 - Patient Details

Patient	Age (years)	Etiology of stricture	Stricture length	Stricture site	Previous procedures
1	50	inflammatory	4 cm	bulbar	nil
2	25	inflammatory	1 cm	bulbar	multiple dilatations
3	15	pelvic fracture	2 cm	membranous	suprapubic cystostomy
4	56	pelvic fracture	4 cm	membranous	suprapubic cystostomy
5	40	inflammatory	3 cm	bulbar	optical urethrotomy
6	48	inflammatory	1.5 cm	bulbar	optical urethrotomy
7	50	inflammatory	1.5 cm	bulbar	nil
8	24	inflammatory	2 cm	bulbar	nil
9	54	inflammatory	1 cm	bulbar	nil

Materials

The surgiSIS grafts, the purpose-specific endoplast graft-carrying balloon device and a set of needles used for placing the sutures that will hold the device in place are the only special pieces of equipment needed. The surgiSIS grafts and the endoplast devices were supplied by Cook urological.

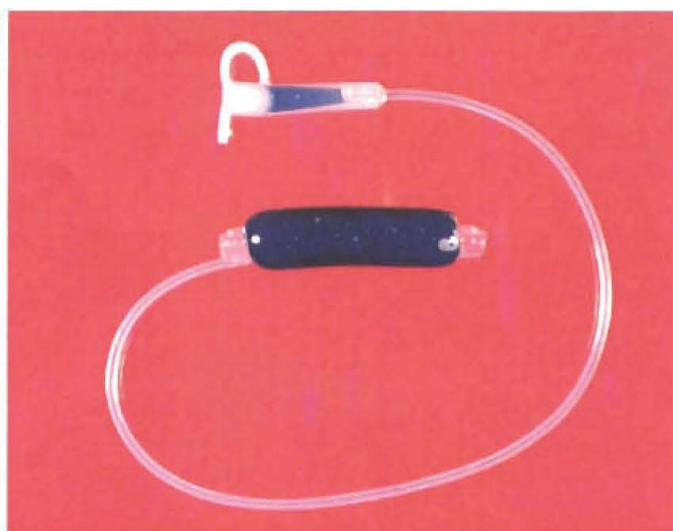
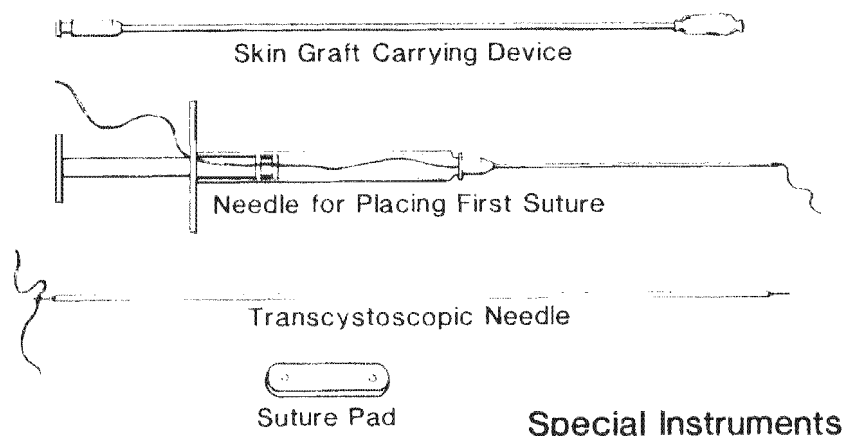
Figure 6 - The endoplast device

Figure 7 - Instruments

Methods

SurgiSIS grafts were used instead of skin in the procedure of endoscopic urethroplasty for the treatment of bulbar urethral strictures. The procedure was performed as follows in all cases:

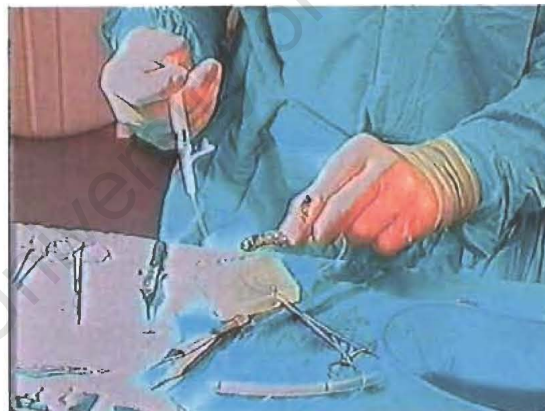
A SurgiSIS grafts was prepared by soaking it in saline for 10 minutes. Multiple small stab incisions were made in the graft with a size 11 scalpel blade. The surgiSIS grafts were tattooed in order to facilitate endoscopic recognition of the grafts at follow up. Tattooing was performed by multiple stabs with a small hypodermic needle filled with India ink. It was noted that tattooing was much less effective than it would have been with skin, because of the paper thin nature of the SIS grafts. The grafts were tubularised over the endoplast graft-carrying balloon device using a running suture of 4-0 polyglycolic acid.

When using full-thickness skin grafts in endoscopic urethroplasty we tie the proximal and distal ends of the tubularised grafts very tightly to the shoulders of the graft carrying device with a nylon ligature. This nylon ligature will cut through the full-thickness skin graft within a few days so that the graft stays behind in the urethra when the device is removed. We tested this principal on surgiSIS grafts in the laboratory prior to commencing our study. No matter

how tightly we tied ligatures or even stainless steel wire around the tubularised grafts, they did not cut through in the same manner as skin grafts do. We believe that this is due to the inert acellular nature of surgiSIS. It is not a living graft and therefore will not undergo pressure necrosis.

We subsequently devised a system whereby a polyglycolic acid ligature was tied around the graft at the proximal shoulder of the graft carrying device. At the distal end of the device the end of the tubularised graft was left open and not fixed to the device. This was done in such a way that the device could be advanced into the urethra carrying the graft with it, but when the graft carrying device was subsequently removed it would slip out from the tubularised graft. An analogy would be two paper cups fitted into each other, with the narrow bottom ends of the two cups representing the proximal ends of the device and graft respectively.

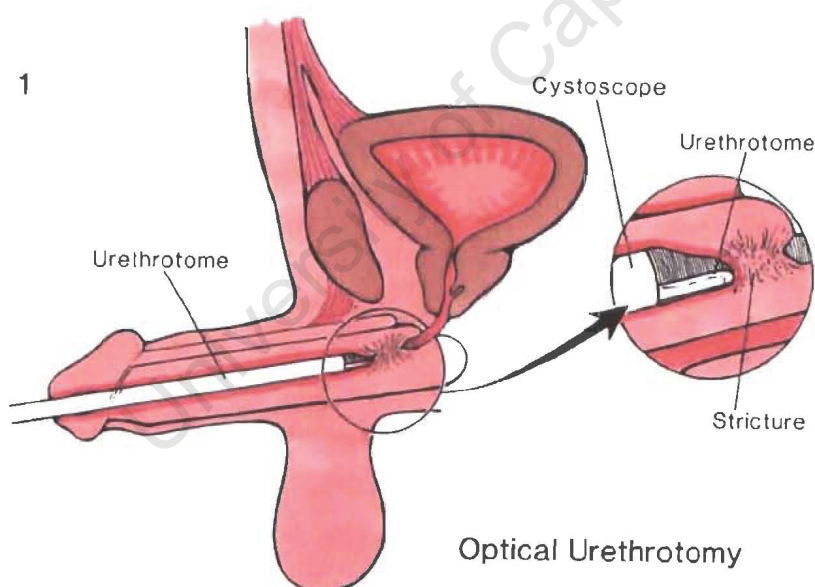
Figure 8 - Preparation of the graft



The graft-carrying balloon device is inflated with normal saline to a soft, jelly-like consistency. The pressure in the inflated device has been previously measured to be 70 to 80cm of water.²⁹ The inflation line is clamped, the inflating syringe is removed, emptied and reconnected to the inflation line. The balloon device can now be aspirated for insertion and reinflated to the desired volume and pressure, by fully depressing the plunger of the syringe. The graft, mounted on the graft-carrying device, is stored in saline.

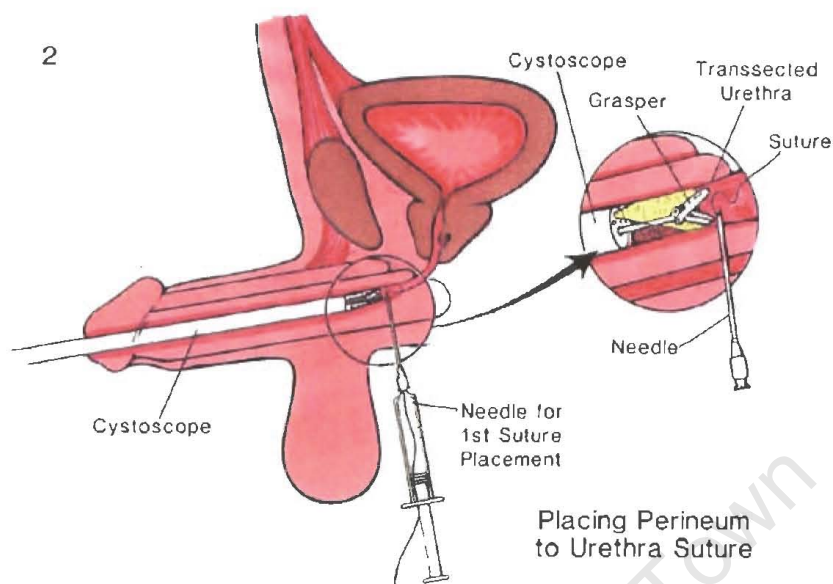
Optical urethrotomy of the stricture is performed and extended for 5mm on either side of the stricture into normal tissue (Figure 9). Full-length internal urethrotomy is performed with the Otis urethrotome to allow easy passage of the graft-carrying device.

Figure 9 - Optical urethrotomy



A 22 gauge spinal needle affixed to a 1ml syringe, with a long 2-0 nylon thread through it, is passed from the perineum to the urethra to emerge in the urethral lumen just proximal to the incised stricture. This is performed under endoscopic control, with a cystoscope containing a grasping forceps within the urethra (Figure 10).

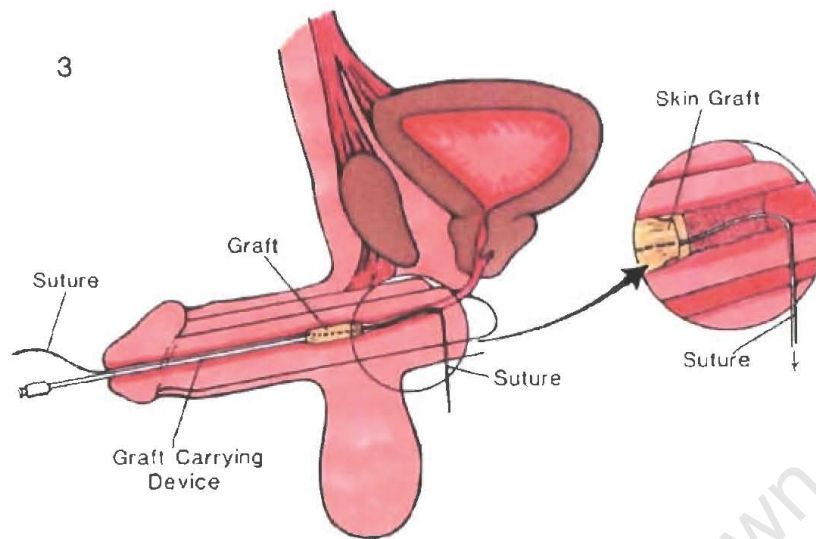
Figure 10 - Placing the perineum to urethra suture



The purpose of the needle-bearing syringe, mounted and loaded with a nylon thread, is to place a suture from the perineum to emerge in the urethra just proximal to the incised stricture. By depressing the plunger of the syringe the nylon thread is made to extrude from the needle tip. This is a single-handed operation, leaving the surgeon's other hand free to manipulate the cystoscope. When the nylon thread extrudes from the needle tip it is grasped with the grasping forceps. The syringe is disassembled and the needle is gently withdrawn from the perineum while a firm grasp is maintained on the thread in the urethral lumen.

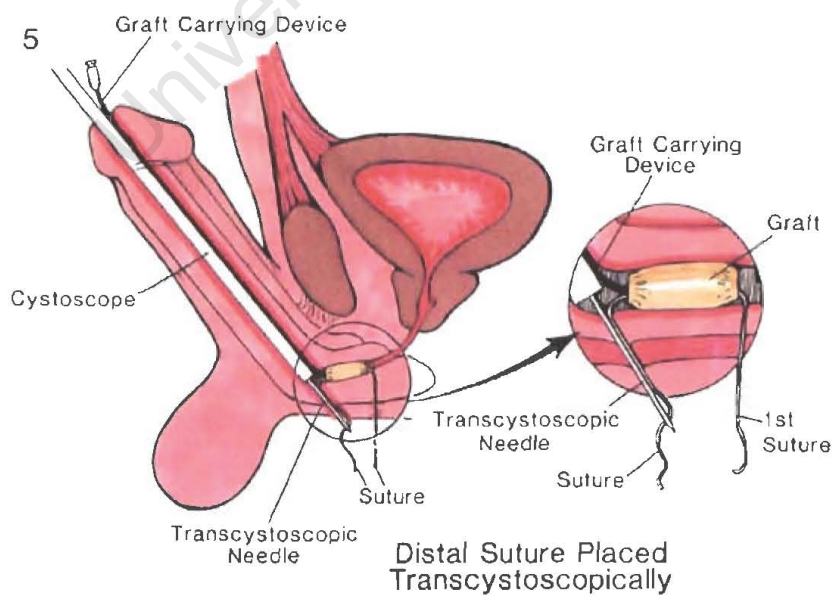
The cystoscope and forceps are withdrawn, pulling the nylon thread along the urethra so that the thread emerges from the external meatus. This perineal-urethral suture is now tied to the proximal end of the graft-carrying device, through a purpose-specific hole in the end of the device. A second 2-0 nylon thread is tied to a corresponding hole in the distal end of the graft-carrying device. While maintaining gentle traction on the nylon suture emerging from the perineum, the graft-carrying device containing the graft is inserted into the urethra and milked down the urethra until it will go no further (Figure 11).

Figure 11 - Positioning of graft and device



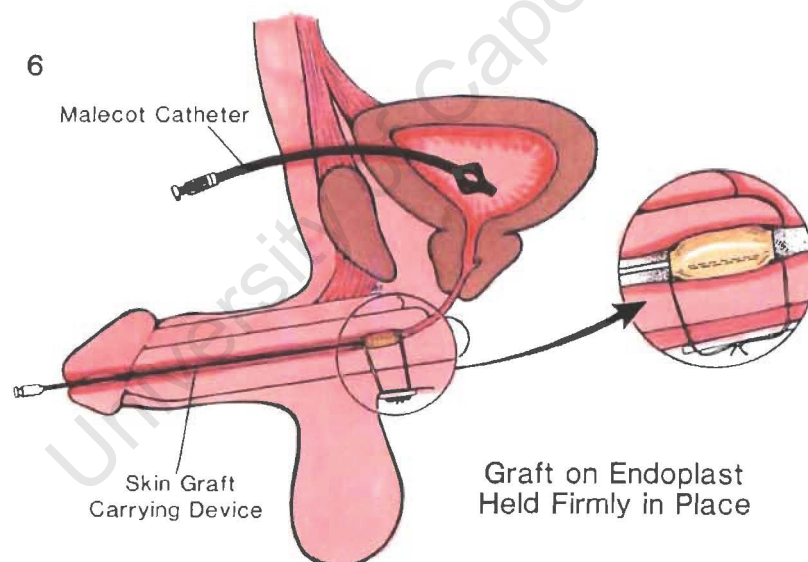
While an assistant maintains gentle traction on the perineal-urethral suture, a purpose-specific transcystoscopic needle is passed and made to pierce the urethra at the distal extent of the graft-carrying device and to emerge from the perineum, where it is grasped (figure 12).

Figure 12 - Placing the urethra to perineum suture



The cystoscope is now removed, leaving the transcystoscopic needle tip emerging from the perineum and its near end (with eye) emerging from the urethral meatus. The second nylon suture, previously tied to the distal end of the graft-carrying device and emerging from the urethral meatus, is tied to the eye of the needle. The needle is pulled through from the perineum, carrying the thread with it. The graft-carrying device is now firmly held in place by a suture at either end, emerging from the perineum. These sutures are tied to each other over a foam backed suture pad (figure 13). The graft-carrying balloon device is now inflated to the correct volume by fully depressing the plunger of the syringe still affixed to the inflation port. The inflation tube is clamped and cut. A small metal plug is inserted into the tube to seal it. Urine drainage is by suprapubic cystostomy.

Figure 13 - End of the procedure



After 10 to 14 days the perineal-urethral sutures are cut and the inflation line is cut in order to empty the graft-carrying balloon device. The device is removed by traction on the inflation line and milking the device from behind forward along the urethra. The device is inspected to see if it contains any of the graft. Once the graft-carrying device has been removed the suprapubic cystostomy catheter is removed and normal micturition is resumed.

Operation Details

The mean operative time was 74 minutes (range 30 – 150 minutes). The two procedures on patient number 3 and patient number 4 with membranous distraction injuries secondary to pelvic fractures were both difficult and took longer to do than the procedures on inflammatory strictures. In patient number 3 bleeding were encountered at the area of the urethral injury. In patient number 4 scar tissue had to be resected with a resectoscope in order to create continuity between the urethral ends and provide a raw area as a graft bed. Resection of this scar tissue caused bleeding that temporarily obscured the view. The mean operative time for the 7 patients with inflammatory strictures was 57 minutes with a range of 30 to 75 minutes. No technical difficulties were encountered in the last 5 patients.

Table 2 - Operation Details

Patient	Stricture details	Operative time (minutes)	Reported difficulty
1	4 cm, bulbar, inflammatory	60	difficulty placing proximal suture
2	1 cm, bulbar, inflammatory	55	difficulty placing proximal suture, bleeding
3	2 cm, membranous, previous pelvic fracture 2 weeks before	120	difficulty due to bleeding
4	4 cm, membranous, previous pelvic fracture 7 weeks before	150	difficulty due to scar tissue and bleeding
5	3 cm, bulbar, inflammatory	75	nil
6	1.5 cm, bulbar, inflammatory	30	nil
7	1.5 cm, bulbar, inflammatory	75	nil
8	2 cm, bulbar, inflammatory	45	nil
9	1 cm, bulbar, inflammatory	60	nil

Follow up

Patients were followed-up by video urethroscopy at 6 weeks and 3 months and micturating urethrography and or flow rate measurement at 6 and 12 months as per protocol, or when symptoms arose. Failure was defined as the need for any further intervention. Long-term follow up will continue, to the point of failure or continued urethral patency (indefinitely).

Results

Patients number two and nine, both with inflammatory strictures, maintained urethral patency without any intervention at one and two years respectively. Patient number nine had a short bulbar stricture with no previous treatment failures and would have been expected to do well with optical urethrotomy alone. Patient number two had undergone many failed urethral dilatations in the past and his success is unlikely to be attributed to the optical urethrotomy alone.

Six patients developed stricture recurrence within six months of surgery. Three of these have undergone subsequent open urethroplasty. Two are currently awaiting urethroplasty and one is maintaining urethral patency with regular self dilatation. One patient was lost to follow-up. Patient number five underwent a dorsal buccal patch urethroplasty after his endoscopic procedure failed. One year later he presented with HIV and clinical AIDS. His HIV status was not known at the time of surgery. No other complications apart from stricture recurrence were encountered.

None of the graft carrying devices contained any graft material at the time of device removal at around 14 days. We tattooed the grafts with India ink in an effort to aid identification during post operative urethrography. In patient number one and patient number five pigmented grafts were clearly seen at follow up urethroscopy. In the other patients it was not possible to clearly demonstrate the presence of pigmentation in the grafted areas. It is unclear whether the grafts failed to take or whether our attempts at tattooing were ineffective. Our impression at endoscopy was that that the grafts did indeed

take, but this would be difficult to prove in the absence of clear endoscopic or histological evidence.

Table 3 - Results

Patient	Endoplast removal	Video urethroscopy 6 weeks	Video urethroscopy 3 months	MCUG 6 months	1 Year	Definitive management
1	uneventful	patent pigmentation seen	defaulted	defaulted	defaulted	Defaulted
2	small amount of graft on device	patent	patent	patent	well maximum flow rate 12.3ml/sec	well max flow rate 10.8ml/sec at 2 years
3	uneventful	patent	stricture in area of repair			anastomotic urethroplasty
4	uneventful	stricture in area of repair	stricture in area of repair			anastomotic urethroplasty
5	uneventful	defaulted	stricture in area of repair, pigmentation seen			dorsal buccal patch urethroplasty
6	uneventful	patent	stricture in area of repair dilated			intermittent self-dilatation
7	uneventful	short stricture in area of repair dilated	short stricture in area of repair dilated			awaiting formal urethroplasty
8	uneventful	stricture in area of repair				awaiting formal urethroplasty
9	uneventful	patent	patent	patent	Voiding well	

Histology

Biopsies were taken from the grafted areas at open urethroplasty in patient number three and number four. Both these patients had membranous strictures secondary to pelvic fractures. In patient number three biopsies were taken at three months after endoscopic urethroplasty and again at open urethroplasty that was performed seven months after the original endoscopic urethroplasty. Histology demonstrated fibrosis in the grafted area and failed to positively identify graft material. In patient number four the open urethroplasty was performed five months after the endoscopic urethroplasty. Histology again demonstrated fibrosis without evidence of graft material being present. It is possible that the SIS grafts had been resorbed by the time of biopsy. In Kropp's canine studies in which bladder augmentation was successfully performed with unseeded SIS grafts there were also no histological evidence of residual graft material in the grafted areas.^{68,69}

Discussion

This study was prompted by our earlier successes with full-thickness skin graft endoscopic urethroplasty and the promising results reported in the literature regarding the use of unseeded SIS as a bladder and urethral graft material in open reconstructive surgery on experimental animals.^{29,65,71,74,75,76} Endoscopic urethroplasty with unseeded surgiSIS grafts was unsuccessful in our study. There are several possible reasons for these treatment failures.

Technically all the procedures were performed without any major mishaps. The two cases performed for membranous urethral injury associated with pelvic fractures took 120 and 150 minutes to perform respectively, as compared to a mean operative time of 57 minutes for the patients with bulbar urethral strictures. In patient number 3 the operation was performed 2 weeks after the pelvic fracture and the difficulty was mainly due to bleeding. In patient number 4 the operation was performed 7 weeks after the pelvic fracture. Scar tissue had to be resected in the region of the urethral injury. This caused bleeding that initially obscured the endoscopic view. Placing a suture from the perineum to the apex of the prostate is

technically more demanding than placing a suture from the perineum into the bulbar urethra. In both these patients the difficulty was caused by the initial bleeding rather than the required position of the suture. Once the bleeding was under control the actual placement of the suture from the perineum to the apex of the prostate was not found to be particularly difficult.

Early attempts at endoscopic urethroplasty were rather crude and failed largely due to excessive movement between the graft and the graft bed, thus causing failure of graft take. Failure of graft take is usually obvious. The grafts tend to be attached to the catheters at removal of the latter.

In our system the two sutures that are tied on the perineum prevent longitudinal movement of the graft carrying device. The inflated balloon secures close apposition between the graft and the graft bed. None of the graft carrying devices contained any graft material at the time of removal. It appeared at initial follow up urethroscopy as if the grafts did indeed become incorporated into the native urethras.

It is possible that minor movements between the graft and graft bed played a role in our failures, but I believe this to be an unlikely explanation. It is impossible to prove retrospectively that no significant movement took place in the graft areas. I do believe that this endoscopic urethroplasty system provides adequate immobilisation and apposition of the graft against the graft bed. Naude used this same graft carrying device and delivery system in his successful operations incorporating full thickness skin grafts.²⁹

When Naude performed his earlier endoscopic urethroplasty procedures using full thickness skin grafts he tested the pressure within the balloon of the graft carrying devices and found this to be 70 – 80 cm water.²⁹ We did not attempt to measure the pressure within the balloons during this study. It is possible that the pressure within the balloons were too high, thus contributing to tissue local ischaemia and subsequent fibrosis.

The processes involved in successful full-thickness skin grafting and tissue regeneration mediated by acellular matrix grafts such as SIS are quite different. Full-thickness skin grafts or buccal mucosa grafts survive by imbibition for 24 -48 hours and then acquire a new blood supply by means of inosculation. This period of graft take takes about four days. The epithelial covering of the potential defect and the high dermal collagen content in a full-thickness graft inhibit wound contraction and scarring. This epithelial covering is believed to be vital for ensuring healing by primary intent and thus preventing scar tissue formation. In endoscopic skin graft urethroplasty a full thickness graft is closely applied to the graft bed created by optical urethrotomy. The graft delivery system and the way it is secured in the urethra prevent any excessive movement between graft and graft bed. This probably explains the excellent results achieved by Naudè in the treatment of inflammatory bulbar strictures and membranous urethral injuries treated early.^{28,29}

When acellular matrix grafts such as SIS is used it is perhaps wrong to talk about "graft take" at all. The graft material is acellular and non viable, and does not actually survive by acquiring a new blood supply. Neither are these grafts dependent on imbibition during the first 48 hours after implantation. The graft becomes incorporated into the native tissues and acts as a scaffold for the regeneration of the host tissue. The grafted area rapidly becomes epithelialised and vascularised, and healing is by tissue regeneration. This process of regeneration is characterised by a mononuclear rather than a polymorphonuclear inflammatory infiltrate, and wound contraction and scarring are usually absent.

Several of the earlier quoted animal studies demonstrated the successful regeneration of the urethra in experimental animals when using unseeded SIS grafts in an onlay fashion.^{74,75} Unseeded SIS grafts were also successfully used in partial ureteric replacement and bladder augmentation in experimental animals.^{68,71,73} Unseeded SIS has proven to be less successful in circumferential urethral replacement.^{76,77} It is unclear why a SIS graft sutured

into the urethra at open surgery should behave differently to a SIS graft that is closely applied to the urethral graft bed following an optical urethrotomy.

Most of the more recent research in the use of matrix grafts such as SIS has focused on cell-seeded grafts. A biopsy is taken from the intended host and by using cell culture techniques epithelial and smooth muscle cells are harvested and expanded in vitro. These cells are then seeded on to a graft such as SIS. A composite graft is thus created in vitro prior to implantation into the intended host.

De Filippo et al compared cell seeded matrix grafts with unseeded matrix grafts in circumferential urethral replacement in rabbits.⁷⁷ In the group treated with unseeded grafts they encountered strictures with fibrosis in all cases. In all of the cases treated with cell-seeded grafts they found widely patent urethras without any fibrosis. De Filippo published his results after we had conducted our study. Histologically the regenerated urethral tissue appeared normal with organised transitional and smooth muscle layers. The regenerated tissue had some capacity for contractility in organ bath studies and cholinergic and adrenergic specific receptors were demonstrated by immunohistochemistry.⁷⁷

The future application of matrix grafts such as SIS may largely be in their role as cell-seeded grafts for urinary tract reconstruction. This certainly is a very exciting area of research. The processes involved however are specialised and cumbersome. It is unlikely that the use of cell seeded matrix grafts will become widespread beyond specialised centres, even if it is proven to be clinically successful. Creating a composite cell seeded matrix graft will probably remain beyond the average urologist practising outside of a specialist centre. On the other hand the prospect of a successful, ready to use, off the shelf graft material would be very attractive.

While endoscopic skin graft urethroplasty with the use of penile or preputial skin has achieved excellent results in inflammatory and iatrogenic strictures of the bulbar urethra and rupture of the membranous urethra treated early, the substitution of SIS for skin has not been successful and cannot be

recommended. The value of seeded collagen grafts in endoscopic urethroplasty remains to be proven. Until such time as it is, and is freely available, preputial or penile skin should be used in this operation.

Conclusion

Endoscopic urethroplasty with unseeded SurgiSIS grafts was unsuccessful in this study and its use can not be recommended.

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