BLADDER AUGMENTATION

- CONVENTIONAL ENTEROCYSTOPLASTY
- CURRENT ALTERNATIVES TO ENTEROCYSTOPLASTY
- THE FUTURE?
  - TISSUE ENGINEERING TECHNIQUES
PEDIATRIC CASE

- 7 YEAR OLD WITH SPINA BIFIDA AND NEUROGENIC BLADDER
- WETTING
- HYDRONEPHROSIS
- HIGH PRESSURE AND LOW CAPACITY BLADDER
- FAILS TO RESPOND TO CONVENTIONAL TREATMENT WITH INTERMITTENT CATHETERIZATION AND PHARMACOTHERAPY

NEUROGENIC BLADDER
Bladder Augmentation
Goals
Increase Capacity
Improve Compliance
Limit Morbidity
Mitrofanoff Procedure

MACE
Bladder Augmentation

Goals

Increase Capacity
Improve Compliance
Limit Morbidity

ILEOCYSTOPLASTY
Conventional Enterocystoplasty

Results

Numerous reports confirming reliable increase in bladder capacity and improve compliance with both ileum and colon
CONVENTIONAL ENTEROCYSTOPLASTY

- Successful
- But along with it comes

Infections

Tumor

Mucus

Perforation

Stones

Metabolic & Bone Growth

PERFORATION

- Life threatening complication
  - 7 reported deaths
- Exact incidence unknown
  - 7 - 15% ? Higher in colon
- Risk factors
  - Overdistension secondary to poor patient compliance
  - Bladder hyperreflexia
  - Chronic infections
- All segments at risk
- High index of suspicion
TUMORS

- Less than 30 cases reported
- Most of the cancers occurred in patients that had tuberculosis or chronic cystitis
- Anastomotic suture line at greatest risk
- “Lag time” greater than ten years
- Recommend surveillance cystoscopy after ten years

TUMORS
INDIANA SERIES

- 260 cases
- All with greater than 10 year f/u
- 3 patients with Metastatic TCC
- Mean time from augmentation 19 years
- Overall cancer risk 1-2%
- ?? Risk greater with time

Soergel et al, 2004
BLADDER AUGMENTATION
PRE-OPERATIVE COUNSELING

- IS SURGERY ELECTIVE?
- EXTENSIVE DISCUSSION OF POTENTIAL COMPLICATIONS OF AUGMENTATION
- COMPLETELY COMPLIANT PATIENT
- MOST SATISFIED PATIENT IS A WELL EDUCATED PATIENT
- QUALITY OF LIFE IMPROVEMENT?

Goals reached with Conventional Enterocystoplasty

- Increase capacity --- YES
- Improve compliance -- YES
- Limit Morbidity -- NO
The Problem: Intestinal Epithelium

“I see the outline for a great article in a medical journal.”

- Conventional Enterocystoplasty
- Autoaugmentation
- Gastrocystoplasty
- Ureterocystoplasty
- Seromuscular enterocystoplasty

?? TISSUE ENGINEERING ??
GASTROCYSTOPLASTY

• First reported in 1956\(^1\)
• Popularized by Mitchell in pediatric patients\(^2\)

1Sinaiko Surg Gyn Obstet 102: 1956

Gastrocystoplasty
Results

■ Stomach vs Intestine\(^1\) -- Urodynamics
  ■ Both improve compliance, but smaller volume reservoirs with stomach
  ■ Phasic sinusoidal contraction / “mass contractions” common with stomach

■ Indiana Series
  ■ 10 % re-augmentation rate\(^2\)

\(^1\)Kilic et al. Eur J Ped Surg 9: 1999
\(^2\)Pope et al. J. Urol ‘98
Gastrocystoplasty
Hematuria – Dysuria syndrome

- Seattle’s Long Term F/U (mean 8 yrs)
  - 24 % had H-D syndrome
- Symptoms from H-D syndrome
  - 35 % sensate urethra
  - 9 % insensate urethra
- Gastrocystoplasty remains viable option
  - Cloacal extrophy
  - Limited amount of bowel
  - “Composite” Augmentation

Plaire et al. J. Urol 2000

AUTOAUGMENTATION

- Creates a large bladder diverticulum

Cartwright and Snow J Urol 142: 1989
Autoaugmentation
Cartwright & Snow (N=30)

- 1/3 increased capacity
- 2/3 improved compliance
- 23% required secondary augment
- Trends - Good results
  - Near normal capacity but poor compliance
- Trends - Poor results
  - Bladder Exstrophy
  - Multiple prior bladder operations


Autoaugmentation
Long term f/u in children

- 17 patients – average age 10 years\(^1\)
- All with spinal dysraphism
- Mean f/u 75 months
- 71% clinical failures
  - Upper tract deterioration
  - Persistent incontinence
- 93% urodynamic failures

\(^1\)MacNeil et al. 2003
Autoaugmentation
Results - Adults

- Results more predictable in adults\(^1\)
- Except for patients with Myelodysplasia\(^2\)
  - (40 % success)
  - ? Irreversible changes to bladder wall in myelodysplasia

\(^1\)Stohrer et al. 1995, 1997
\(^2\)Leng et al. 1999

SEROMUSCULAR ENTEROCYSTOPLASTY
Combines autoaugmentation with a demucosalized flap of colon or stomach
SMEC
Results - Stomach and Colon

- Dewan, PA, Dial Ped Urol 22: 1999
  - All showed increased capacity
  - 1 pts required ileocystoplasty
- Carr et al. J. Urol 162: 1999
  - 38 % successful
  - 30 % re-augmentation
  - Increased capacity 1.8 times
  - 22 % hour-glass deformity, 13 % failure
  - 5/7 bx showed colonic mucosal regrowth

Seromuscular
Intestinocystoplasty

- Lima Experience (Brazil)
  - 129 patients (Mean f/u 51 months)
  - Use of both ileum and sigmoid
  - Excellent increase in capacity and compliance
  - Minimal to no mucus, no cases of tumors
  - 10% reaugmentation rate
- Reasons for success:
  - Methods of demucosalization?
  - Use of post-operative balloon / mold?
URETEROCYSTOPLASTY

- First described by Eckstein\(^1\)
- Popularized in early ‘90’s \(^2,3\)

\(^1\)Eckstein and Martin. Act Urol 4: 1973
\(^2\)Churchill et al. J Urol 1993
\(^3\)Bellinger, M.F., J. Urol 1993

Ureterocystoplasty
Preliminary Reports

- All had increased capacity (40-800%)
- When distal ureter used only: less reliable increase in capacity and compliance group
- Initial reports: No repeat augmentations to date
Ureterocystoplasty

Results

- Single Distal Ureter (22 pts)
  - Mean increase in capacity 177% (11-560%)
  - Only 50 % reached or exceeded age expected capacity
  - Long term complications (n=1 each)
    - Deterioration of bladder compliance
    - Spontaneous perforation requiring enterocystoplasty

Pascual et al. J. Urol 2001

URETEROCYSTOPLASTY

PREDICTIVE FACTORS FOR SUCCESS

- Multi-institutional study
- 64 patients
- Evaluation of pre-operative status and urodynamic studies

Husmann et al, 2004
URETEROCYSTOPLASTY
PREDICTIVE FACTORS FOR SUCCESS

- Patients without reflux
  - Success directly related to pre-op diameter of ureter (> 1.5 cm with good results)

- Patients with reflux
  - Preoperative urodynamics predictive of success when good compliance noted (including refluxing ureter), but further big increases in capacity and compliance post-op not noted
  - Poor success if pre-op urodynamics with poor compliance (including refluxing ureter) – nearly all patients requiring reaugmentation

Husmann et al, 2004

BLADDER AUGMENTATION
WHERE ARE WE NOW?
The use of bowel for bladder augmentation is still the **GOLD STANDARD**
WHERE DO WE GO FROM HERE??
“THE ABILITY TO REPLACE ABNORMAL TISSUE WITH REGENERATED NORMAL TISSUE WILL REVOLUTIONIZE MEDICINE AS WE KNOW IT TODAY”
BRIDGING THE GAP

BASIC SCIENCE

CLINICAL PRACTICE
Tissue Engineering
UROLOGY TISSUE NEEDS

- CONGENITAL DEFECTS
  - BLADDER
  - URETER
  - GENITALIA / REPRODUCTIVE SYSTEM
    - PENIS / CORPORAL BODIES
    - VAGINA / UTERUS
- KIDNEY / RENAL FAILURE
- CANCER

Tissue Engineering

The FUTURE of GU organ replacement

- BLADDER
  - Urethra
  - Ureter
  - Penis / Corporal bodies
  - Vagina
  - Uterus
TISSUE ENGINEERING TECHNOLOGY

**TECHNIQUES:**

“UNSEEDED”

“SEEDED”

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TISSUE ENGINEERING TECHNOLOGY

- **Unseeded Technique:**
  - Biomatrix or synthetic material transplanted into host organ
  - Host utilizes biomatrix or synthetic material as template for ingrowth of new cells and initiation of tissue regeneration and eventual organogenesis
UNSEEDED TECHNIQUE

Biomatrix promotes regeneration directly

UNSEEDED TECHNIQUE

History

- SYNTHETIC (non-biodegradable, 50’s and 60’s)
  - Silicone, PTFE, Polypropylene
- Biodegradable (70’s and 80’s)
  - Rice paper, Vicryl, Placenta, Amnion, Pericardium
Unseeded Techniques

MATERIALS (90’s)
- Small Intestinal Submucosa (SIS)
- Bladder Acellular Matrix Graft (BAMG)
- Bladder Acellular Matrix Allografts (BAMA)

Small Intestinal Submucosa (SIS)
- Submucosal Layer of Pig Intestine (Sausage Casing)
- Collagen with Intrinsic Growth Factors (TGFβ, bFGF, GAG)
- Promotes regeneration (blood vessels, ligaments, skin, GU organs)

Stephen Badylak, M.D., Ph.D., DVM. ‘87
Small Intestinal Submucosa (SIS)

- Rat and Canine partial cystectomy models (15 months)
- Regeneration of urothelium, submucosa, smooth muscle layer
- normal capacity and compliance
- Muscle to Collagen ratio decreased

Kropp et al., World J. Urol '98
SIS
WHY IS IT DIFFERENT?

- NON SYNTHETIC
- INHERENT AND FUNCTIONAL GROWTH FACTORS
  - TGF-beta
  - bFGF
  - VEGF
SIS
POTENTIAL LIMITATIONS

- COMMERCIALY AVAILABLE FORM (SURGISIS AND STRATASIS, COOK BIOTECH)
  - MATERIAL ALTERED IN ITS REGENERATIVE CAPABILITIES
  - HAS NOT PRODUCED SAME REGENERATIVE RESULTS AS ORIGINAL MATERIAL
  - DIFFERENT PROCESSING
  - ONGOING RESEARCH
CLINICAL APPLICATION OF SIS FOR BLADDER AUGMENTATION

SIS CLINICAL APPLICATIONS (GU)

- Sling material
- Corporal body grafting (Penis)
- Renal capsule
- Parastomal and Ventral Hernias
- Urethral Fistula Barrier
Bladder Acellular Matrix Grafts (BAMG)

- Morphologic regeneration of urinary bladder in the rat model
- Regenerated bladder had functional characteristics similar to normal rat bladder

Sutherland et al. J. Urol ‘96

Bladder Acellular Matrix Allografts (BAMA)

- Porcine model, 3 months
- Results
  - Repopulation with all native cellular components
  - Normal capacity and compliance

Reddy et al. AAP abstract ‘99
TISSUE ENGINEERING
UNSEEDED TECHNIQUE

- FUNCTIONAL BLADDER REGENERATION IS POSSIBLE
- SEVERAL BIOMATERIALS AVAILABLE
- POTENTIAL LIMITATIONS:
  - SIZE AND AMOUNT OF REGENERATED TISSUE
  - EFFECTS OF TERMINAL STERILIZATION MAY REDUCE REGENERATIVE CAPACITY
  - INAPPLICABLE TO CASES OF TOTAL OR NEAR TOTAL ORGAN REPLACEMENT
  - VARIABILITY IN BIOLOGIC MATERIAL WITHIN MATERIAL

SEEDED TECHNIQUE
TISSUE ENGINEERING:
SEEDING TECHNIQUE

- PRIMARY CELLS DERIVED FROM BIOPSY
- CELLS SEPARATED AND EXPANDED *IN VITRO*
- CELLS SEEDING ONTO BIOMATRIX OR SYNTHETIC MATERIAL
- CELL / MATRIX COMPOSITE PLACED BACK INTO HOST FOR CONTINUED REGENERATION
- IN COMPARISON TO UNSEED TECHNIQUE: “JUMP STARTS” REGENERATIVE PROCESS

SEEDING TECHNIQUE

- Biomaterial acts as a cellular transport vehicle
- Materials
  - PGA / PLGA
  - SIS
Primary Human Urothelial Cells

Primary Human Smooth Muscle Cells
SEEDING TECHNIQUE
PGA / PGLA POLYMER

- 11 mo Canine subtotal cystectomy model
- UNSEEDED: Marked contraction with little evidence of regeneration
- SEEDED: Results with seeded PGA were excellent
- CONCLUSION: SEEDING OFFERS SIGNIFICANT ADVANTAGES (SYNTHETIC MATERIAL)

Oberpenning et al. ‘99
SEEDING OR UNSEEDING TECHNIQUES:

REGENERATED BLADDER ➔ NORMAL BLADDER

CELLS ← BIOMATRIX

HOST
BLADDER TISSUE ENGINEERING PROBLEMS

- LACK OF REGENERATION OF COMPLETELY NORMAL FUNCTIONAL ORGAN
- INADEQUATE UNDERSTANDING OF REGENERATIVE PROCESS
- WITH BOTH SEEDED AND UNSEEDED TECHNIQUES: STUDIES THUS FAR IN ANIMAL MODELS WITH A NORMAL BLADDER

![Diagram showing regeneration of normal bladder](image)
HUMAN SMOOTH MUSCLE CELLS
Normal vs. Neuropathic

Neuropathic Cells IN VITRO
- Increased *in vitro* proliferation
- Decreased *in vitro* contractility
- Less cellular adhesion

NORMAL AND NEUROPATHIC BLADDER SMOOTH MUSCLE CELLS

A  B
Cell Proliferation

Days
0 1 3 5 7 10

Cell Count
0 10000 20000 30000 40000 50000 60000 70000

Normal
Neuropathic

A-II Mitogenesis

% Positive Control
0 10 20 30 40 50 60

Normal
Neuropathic

Mitogen
All
All + Los
Serum Deficient

*
FIGURE 5: Contraction of normal and neuropathic In comparison to 10% serum conditions, there is a significant with LPA (*, p< .05), Ca-Ionophore, (**, p< .05) and minimal to no contraction to carbachol and angiotensin II (A-II). The majority of contraction occurs within the first 10 minutes after release of the lattice. See Figure 6

SIGNIFICANCE

- The functional implications of these findings needs to be investigated
- These results raise concerns about the use of neuropathic bladder SMC for tissue engineering
- Genetic manipulation of abnormal SMC may have to occur prior to successful clinical use for tissue engineering
CURRENT LAB FOCUS

- Improve current techniques for regeneration
  - Nanotechnology
- Address concerns re: use of neuropathic cells
  - Increase understanding of differences
  - Alternative cell sources
- Better mechanistic understanding of the regenerative process
NANOTECHNOLOGY

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BIOSCAFFOLDS

- BIOLOGIC (SIS, BAMA, BAMG)
  - INHERENT BIOLOGIC ACTIVITY
  - INCONSISTENCIES AND INHERENT VARIABILITY IN MATERIAL
- SYNTHETIC (PGA / PLGA)
  - CONSISTENT IN CONTENT
  - LACK INHERENT BIOLOGIC ACTIVITY
  - LACK OF OPTIMAL FRAMEWORK FOR CELL ATTACHMENT AND GROWTH
  - TOO POROUS
NANODESIGNED SCAFFOLDS

- SYNTHETIC SCAFFOLD
- NANODESIGNED TO ACT MORE LIKE A MORE BIOLOGIC MATERIAL
- “SMART” SCAFFOLD
- CONTROLLABLE AND PREDICTABLE ACTIVITY
- CONSISTENT IN CONTENT AND BIOLOGIC RESPONSE

Self-Assembling Peptide-Amphiphiles

- Hydrophobic tail: drives self-assembly
- X-linker: covalent capture of assembled fibers
- Biorelevant peptidic segment: cell recognition of signals for adhesion, spreading, etc. (e.g. RGD)

Porous Biodegradable Cell Scaffolds

- PGA /PLGA scaffolds
- COATED WITH SPECIALLY DESIGNED SELF ASSEMBLING (PA) UNITS WITH GROWTH FACTOR BINDING SITES

Scaffold Model in Tissue Engineering

- isolation of primary cells from healthy tissue
- in vitro proliferation
PA COATED SCAFFOLDS
RGD BINDING SITE

BARE

COATED

100 µm
Growth Factor Delivery from Nanofiber Gels

Heparin-tether  Phage-display

Apply PA technology to bladder tissue engineering through the binding and release of relevant growth factors

Cell Entrapment within Gel-Scaffold Composite

PGA fiber scaffold is partially submerged in a suspension of PA and SMCs in cell media.

PA solution forms a gel around PGA scaffold, entrapping cells.

Gel-scaffold composite is removed from well and flipped for second layer.

Suspension of PA, urothelial cells, and cell media fill remaining interstices.

Final SMC-urobilayer structure
WILL IT WORK???

TISSUE ENGINEERING
ALTERNATIVE CELL SOURCES

- STEM CELLS
  - EMBRYONIC STEM CELLS
  - PERIPHERAL STEM CELLS
    - BONE MARROW
    - FAT
    - BLOOD
BLADDER TISSUE ENGINEERING
CONCLUSIONS

- TREMENDOUS POTENTIAL TO REVOLUTIONIZE URINARY RECONSTRUCTION
- BOTH SEEDED AND UNSEEDED TECHNIQUES WILL HAVE A ROLE
- ALTERNATIVE CELLS SOURCES ATTRACTIVE

BLADDER TISSUE ENGINEERING
CONCLUSIONS

- FIELD STILL IN ITS INFANCY
- FUTURE ADVANCEMENTS AND SUCCESS WILL DEPEND ON A GREATER UNDERSTANDING OF THE EXACT CELLULAR MECHANISMS AND FACTORS THAT ARE INVOLVED IN THE REGENERATIVE PROCESS ON A NANOTECHNOLOGY LEVEL
“THERE ARE SOME THINGS IN LIFE THAT WE MAY NOT BE ABLE TO CHANGE!”
"Whoa! Watch where that thing lands — we'll probably need it."
THANK YOU !!!!