

Histology of First Generation BioMesh

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Ideal Implant

- Readily available and affordable
- Biocompatible and chemically inert
- Noncarcinogenic
- Strong, sterile
- Minimal risk of infection or rejection
- No detrimental effect on pelvic function
- More durable than autologous tissue

Host Response to Graft: Translational

- NO graft materials biologically inert
- Foreign body response REGARDLESS of material.
- Variable biofilm forms (important)
- Influx of proteins follows (immunoglobulins / fibrinogen)
- Proteins undergo conformational change
 - Bind antibodies, macrophages and fibroblasts and *Neovascularization* then occurs

Genetic Expression & Mesh “Rejection”

- Warsaw, Poland (1/02-9/05)
- 830 Polypropylene Mesh Insertions
- 4.5% Erosions
- 37 Cases vs 300 Controls Screened Preoperatively for IL-2, IL-4, IL-5, IL-10, INF alpha and INF gamma
- **Significant Increase in INF gamma in Cases ($p < 0.04$)**

Tissue Ingrowth

- Orderly arrangement of collagen fibers and connective tissue facilitates ingrowth of host tissue.
- If an intergration of host tissue occurs, the implant retains it's strength
- *Does irradiation or freezing effect this arrangement?*

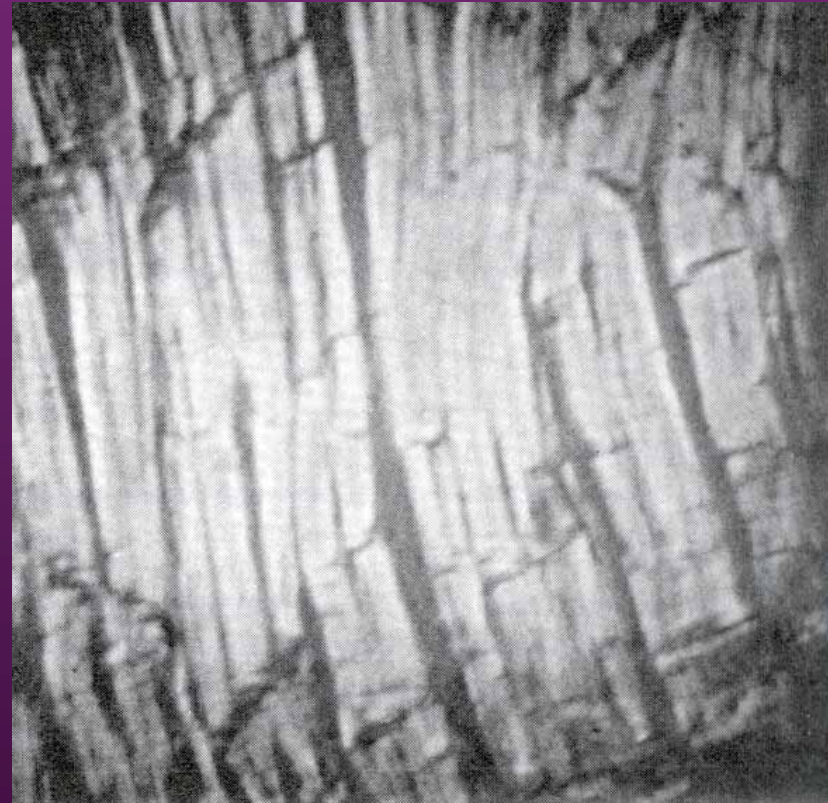


Photo: Kim H, et al: Urology 58: 800-804, 2001

Host Tissue Ingrowth

- Neovascularization and fibroblasts infiltrate at periphery and superficial surfaces of the graft.

Curtis R, et al: Am J Sports Med 19:408-415, 1985.

Defrere J, Franckart A: Clin Orthop Rel Res 303:56-66, 1994.

Lamme E, et al: J Pathol 190:595-603, 2000

- Central portion of graft acellular for years.

Malinin T, et al: Arthroscopy 18:163-170, 2002

- Once entire graft infiltrated, transformation process is completed.

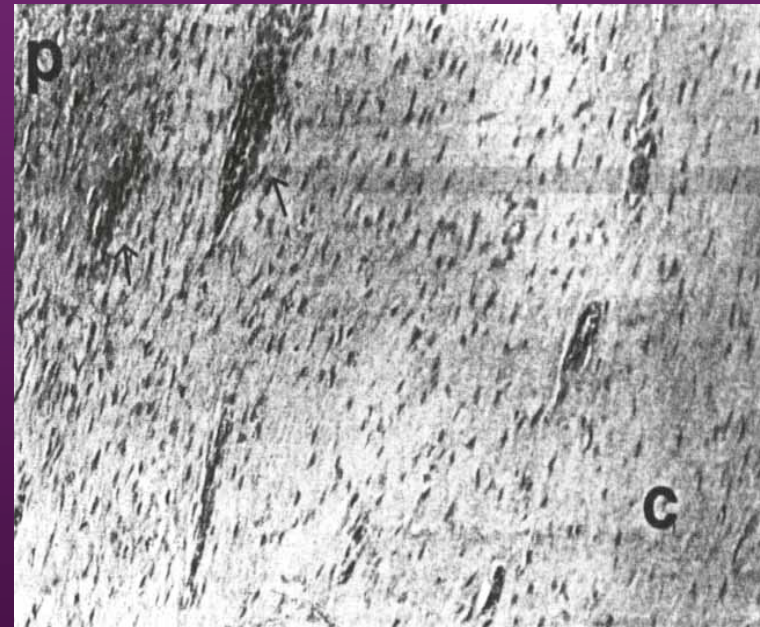
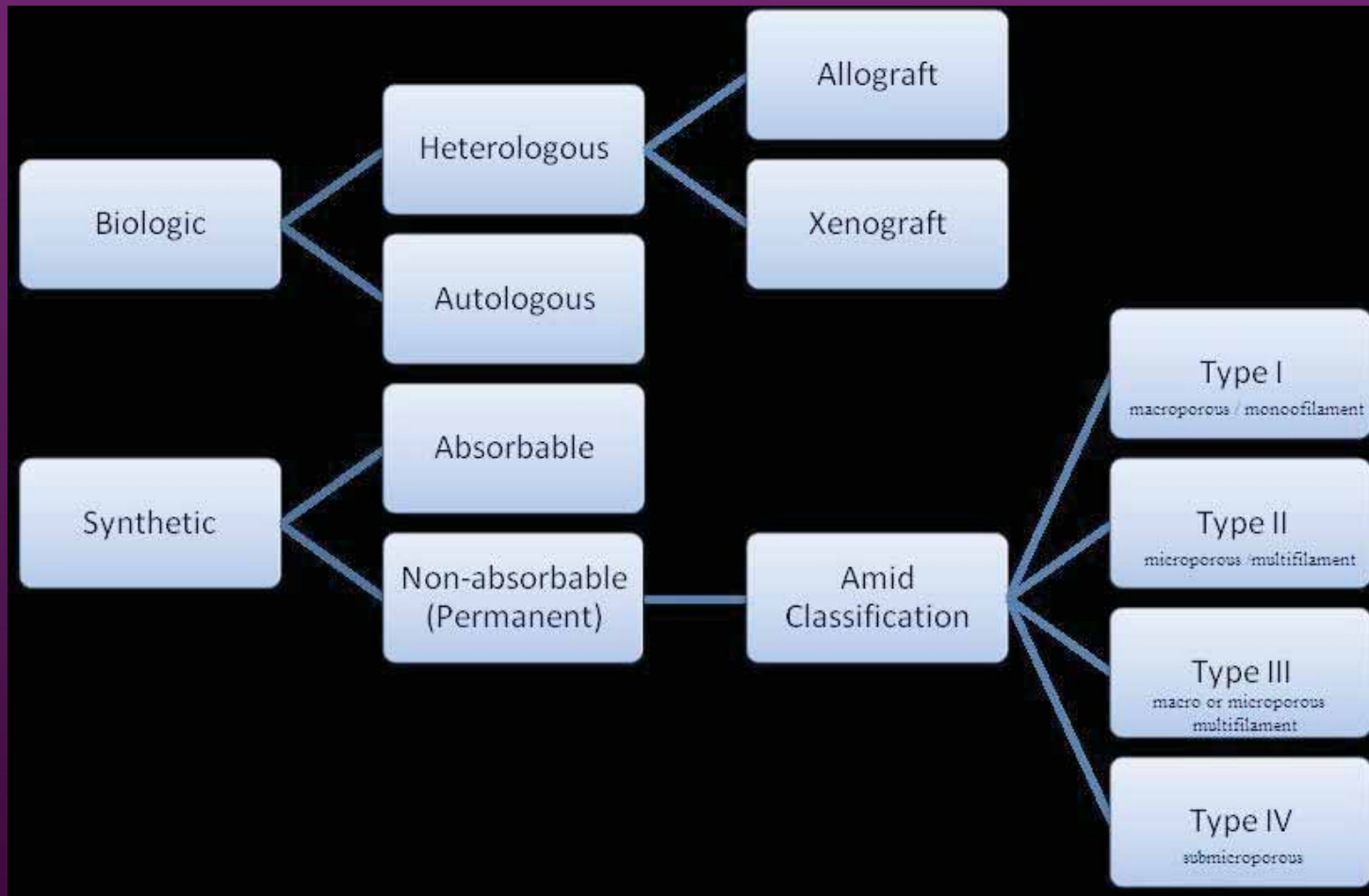


Photo: Nikolaou P, Am J Sports Med 14: 348-360, 1986.

Host Tissue Incorporation

- It appears that for long-term graft survival, host tissue incorporation must occur to facilitate a process of graft remodeling, “transformation” into host.
- Even for permanent materials!!!
- “Graft remodeling”

Classification of graft materials



Biologic Materials

- ***Allografts***

- **Cadaveric Fascia Lata**
 - Freeze Dried
 - Solvent Dehydrated
 - Tutoplast®
 - Irradiated
 - Cryopreserved.
- **Dermis (Basement Membrane)**
Repliform®
- **Dermis (No Basement Membrane)**
DuraDerm®
Urogen®

- ***Xenografts***

- Porcine Intestinal Submucosa
Stratisis®
- Porcine Dermis
Dermatrix®
Pelvicol®
- Bovine Pericardium
Tissue-Guard®

Processing of Graft Material

- Federal guidelines direct the harvesting and transplantation of tissues.
- No guidelines for tissue processing and packaging:
 - Sterilization: Proprietary process to destroy bacteria and viruses.
 - Packaging:
 - Frozen
 - Freeze-dried
 - Solvent Dehydrated
 - Cryopreservation

What happens to graft material after implantation?

- Potential mechanisms for failure:
 - Tissue failure (rupture)
 - Tissue rejection
 - Tissue degeneration.

It appears that tissue remodeling is necessary for long-term implant durability.

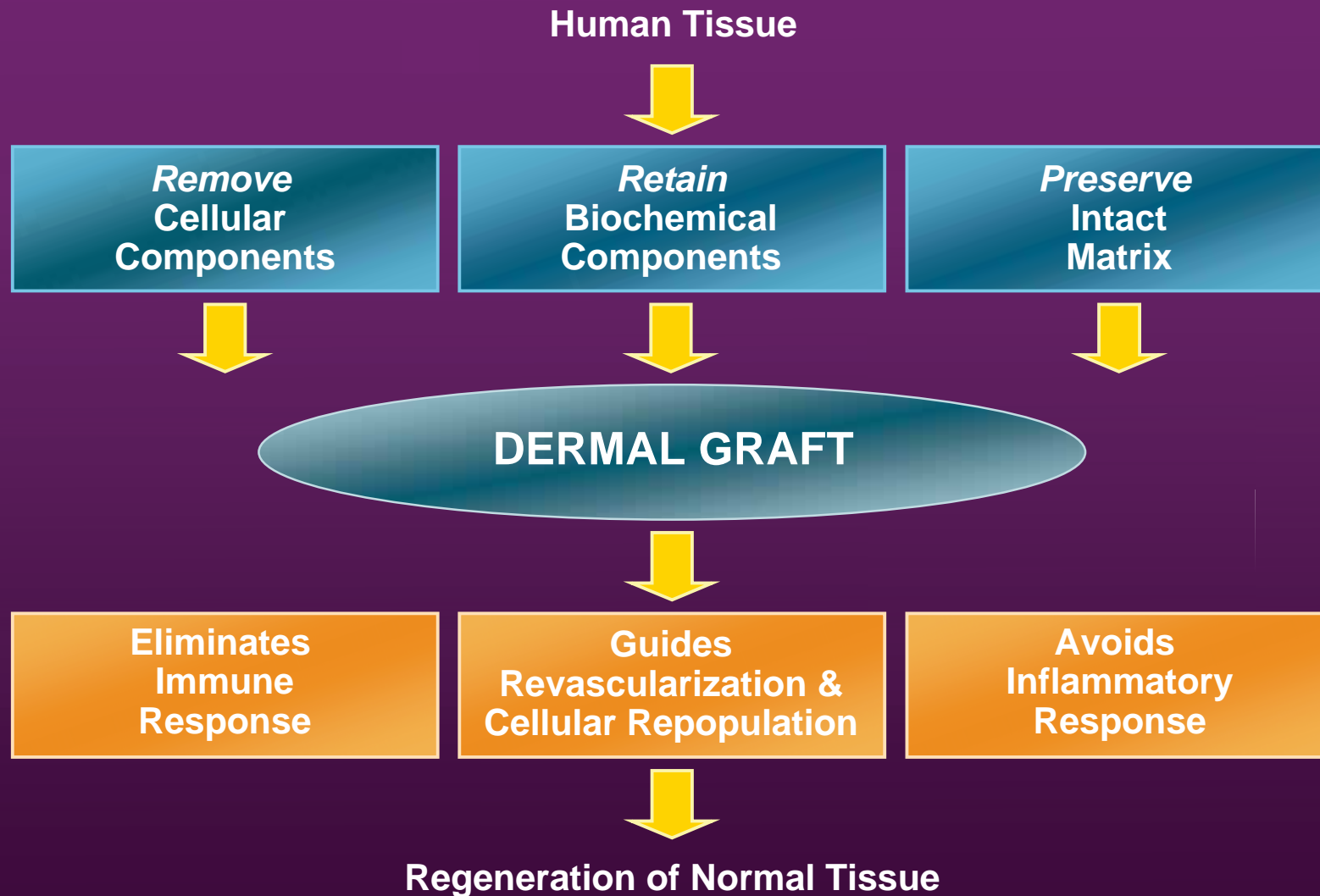
Tissue Failure

- Much early emphasis placed on biomechanical comparison of graft strength.
 - Biomechanical testing endpoints:
 - Stiffness [elongation (displacement) of material during load]
 - Maximum load to failure
- Major limitation is that testing process does not replicate forces placed on sling after implantation.
- Little data demonstrating graft rupture as mechanism of failure.

Tissue Rejection

- Very little data demonstrating host rejection of allograft.
- Inflammatory cells around allograft more commonly represent generalized inflammation, not rejection.

TEMPLATE FOR REGENERATION

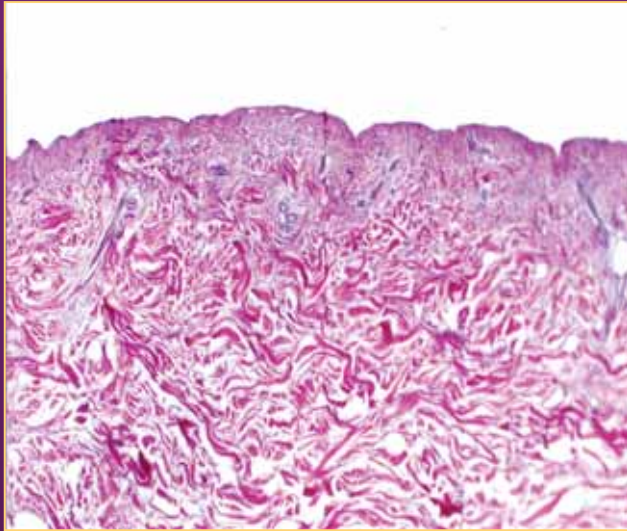


COURTESY OF REPLIFORM

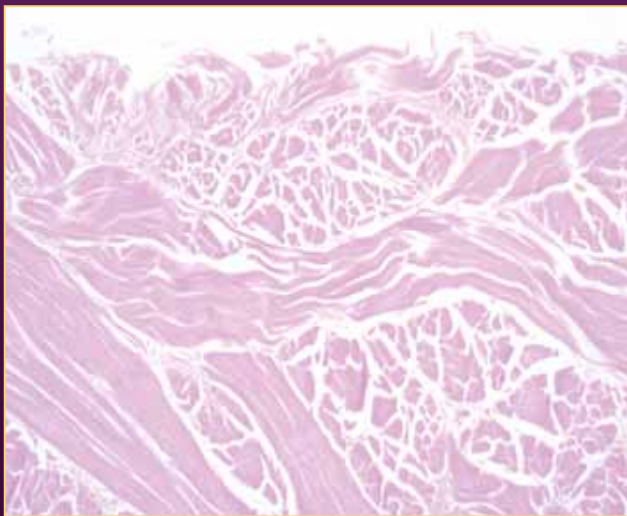
Human versus Porcine

	Repliform	Porcine
Tissue Origin	Human	Pig
Processing	Minimal	Extensive
Cell Remnants	Rare	Rare
Basement Membrane	Present	Absent
Elastin	Abundant	Scarce
Biochemistry	Natural and consistent with normal human dermis	Chemically altered by cross-linking
Sterilization	Not required	Required
Fate of the graft	Incorporated & Remodeled	"Permanent"

Histological Comparison of Human and Porcine



Human Dermis
H&E stain



Porcine
H&E stain

Xenografts

- Porcine dermis most frequently utilized.
- Allografts supply limited
- Standardized preparation methods decrease variability of grafts.

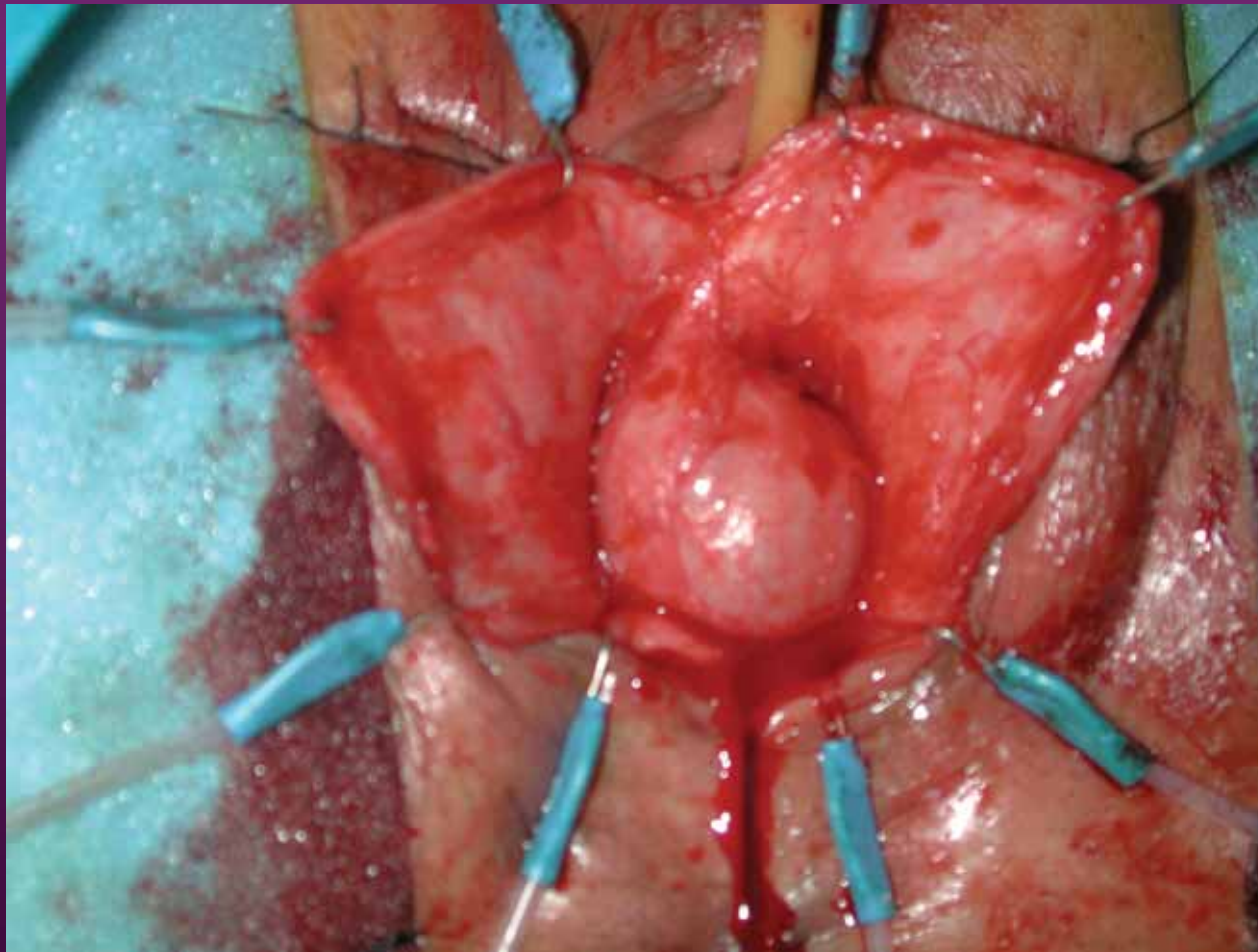
- Most commonly utilized of biologic materials
- Fenestrated grafts facilitate incorporation

Intexen™ & Pelvicol™

Attribute	InteXen	Pelvicol
Average Thickness*	1.23 mm	0.89 mm
Tensile Strength*	18.4 kgf	14.4 kgf
Suture Retention*	8.3 kgf	5.7 kgf
Storage	Frozen	Room temperature
Preparation	Defrost for 5 minutes; hydrate in saline if not immediately implanted from package	Hydrate in saline if not immediately implanted from package
Handling	Easy to handle; a little stiffer than human dermis	Easy to handle; a little stiffer than human dermis
Preservation	Frozen	Vacuum packed
Sterilization	Gamma irradiation	Gamma irradiation
Material Origin	Porcine dermis from U.S.	Porcine dermis from U.K.
Cross-linked	No	Yes, with HMDI (hexamethylene di-isocyanate)

*Data on file

Anterior Colporrhaphy With Graft Interposition

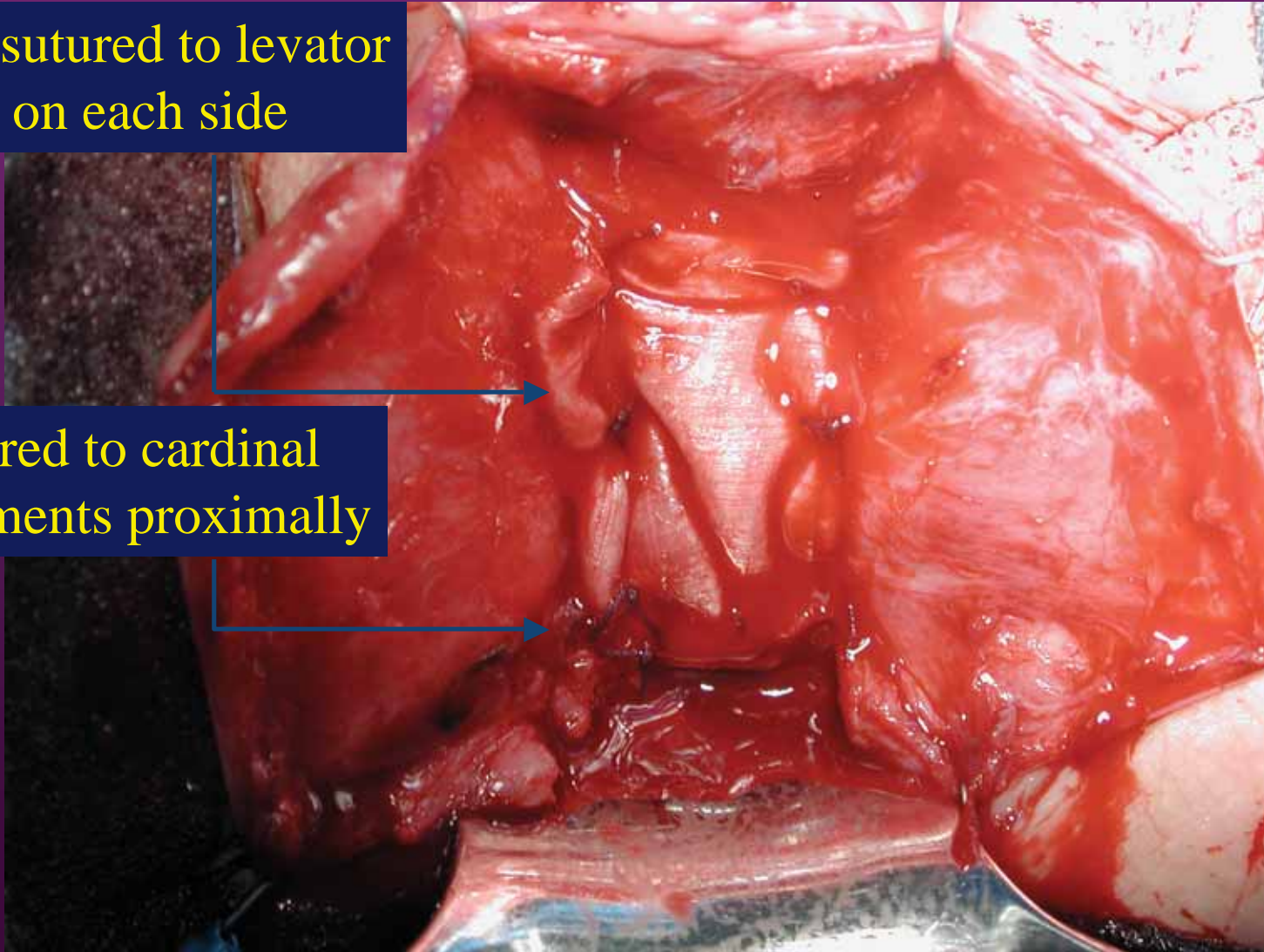


When pubocervical fascia is inadequate for re-approximation consider graft interposition (allograft, xenograft, synthetic)

Anterior Colporrhaphy With Graft Interposition

Graft sutured to levator fascia on each side

Sutured to cardinal ligaments proximally



Augmented Anterior Vaginal Repairs: Prospective RCT of Porcine Dermis

Mean F/U 1 Year (N=201)

11% Recurrent Symptoms

*7% Recurrence in Pelvicol Group (N=98)**

19% Recurrence in Controls (N=103)

Significant Decrease in VAS in Each Group ($p < 0.001$)

1 Woman “Rejected” Pelvicol Graft

- Removed at 1 Month

***P=0.019**

Augmented Anterior Repairs

Prospective RCT: Pelvicol vs Prolene Soft

- Cervigni et al: ICS 2005 Abstract # 118
- N=72 8 Month F/U
- Tension-Free Repair
- 68% Pelvicol Group "Anatomically Cured"
 - 3% Erosions
- 58% Prolene Soft "Anatomically Cured"
 - 8% Erosions
- Prolene Soft Reduced DO ($p=0.02$)
- Pelvicol Improved Compliance ($p=0.02$)

Prospective Trial of Prolift vs VH+ A&P Repair ± Pelvicol

- 160 Women at 1 Year

	VH+A&P N=55	Pelvicol N=53	Prolift N=25	P
Anatomic Cure	14.5%	43%	40%	0.05
Recurrence	64%	42%	44%	0.05
DeNovo Prolapse	26%	15%	16%	0.05
Repeat Surgery	15%	14%	12%	NS

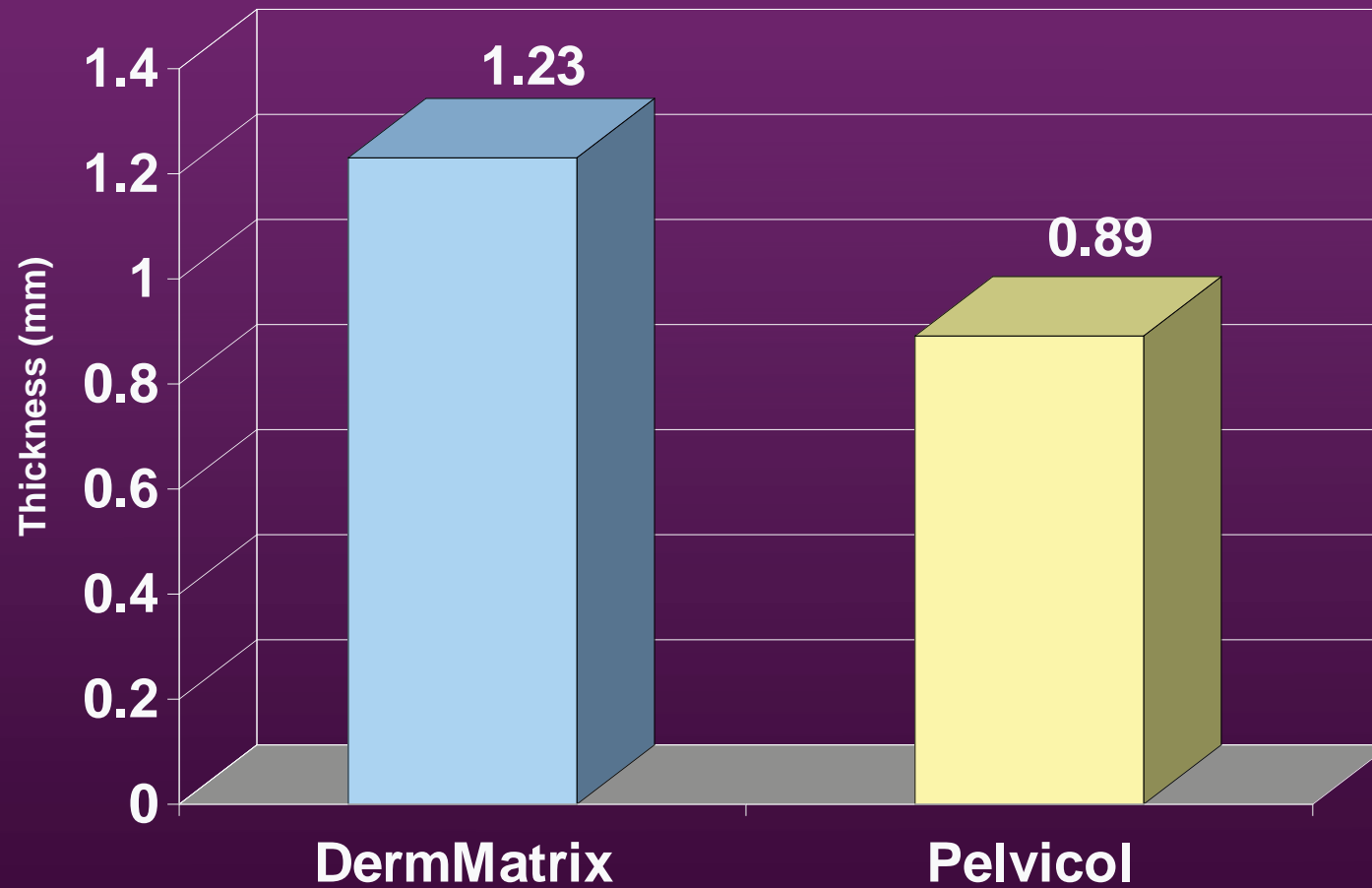
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Average Graft Thickness

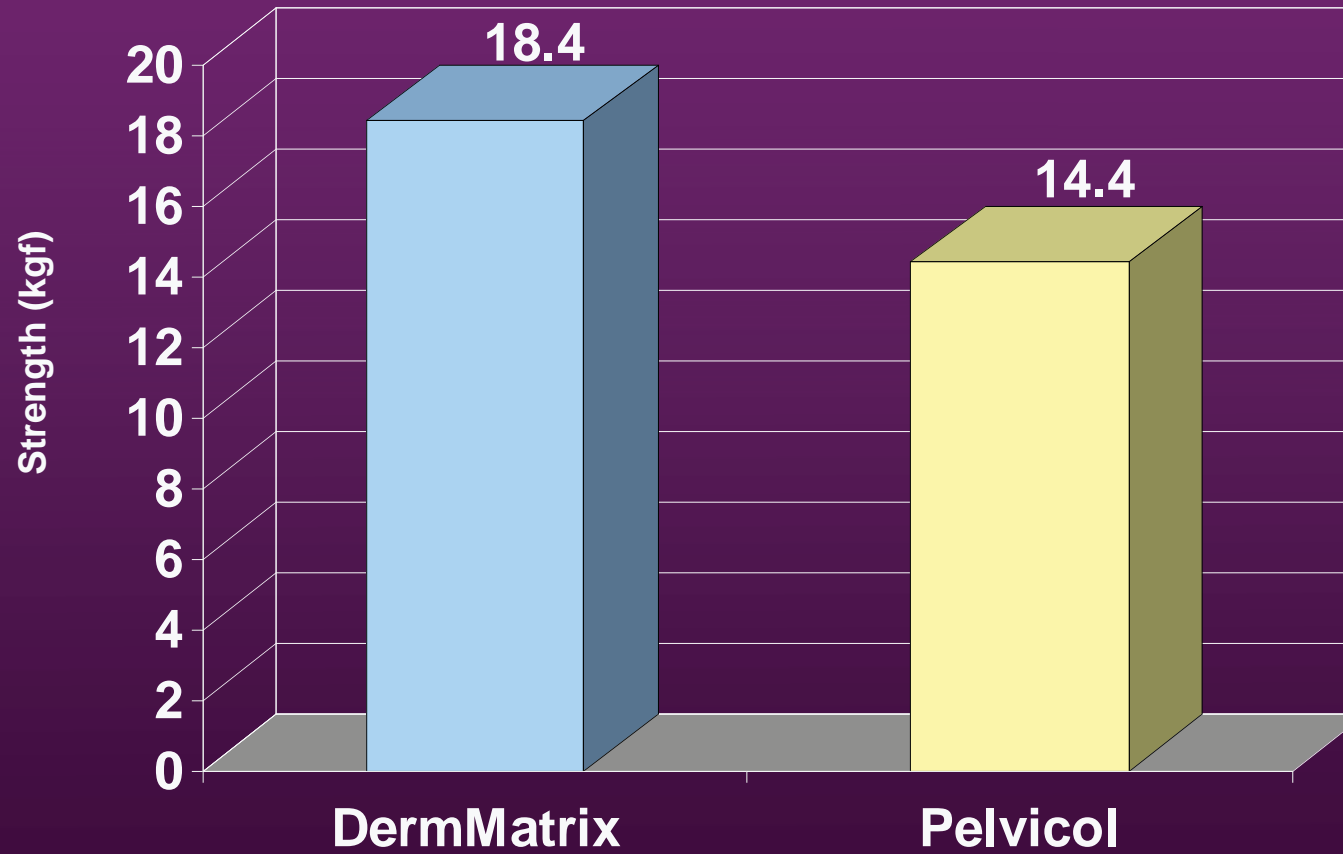
Porcine Dermis



*Data on file American Medical Systems

Tensile Strength

Porcine Dermis



*Data on file American Medical Systems

Advantages of Porcine Grafts

Collagen 95% analogous to human

Non – allergenic scaffold for host in-growth

*Multiple sizes (no longer refrigerated) /
no supply limitation*

Rapid re-hydration

Porcine Dermis as Sling

Short to intermediate results c/w other interventions

J Obstet Gynaecol, 21: 162-165, 2001.

Int Urogynecol J, 14: 17-23, 2003.

Acceptable biocompatibility

No evidence for untoward morbidity

Histopathologic Changes of Porcine Dermal Implants used for Transvaginal Suburethral Slings

*S. Gandhi, L.A. Kubba, Y. Abramov, S.M. Botros, R.P
Goldberg, T.A. Victor, P.K. Sand*

*Evanston Northwestern Healthcare
Northwestern University Medical School*

Histology of HMDI Porcine Dermis

63 Women with HMDI Porcine Sling:

10 Women had urinary retention

Specimens at 6, 15, 19, 21, and 42 weeks

2 Women had recurrent SUI

Specimens at 58 and 67 weeks

1 Control Graft Processed

Histology of HMDI Porcine Dermis Retention Explants (6, 15, 19, 21, & 42 weeks)

Collagen structure almost completely maintained up to 42 weeks after implantation

Layered collagen deposition mostly limited to periphery of the implants

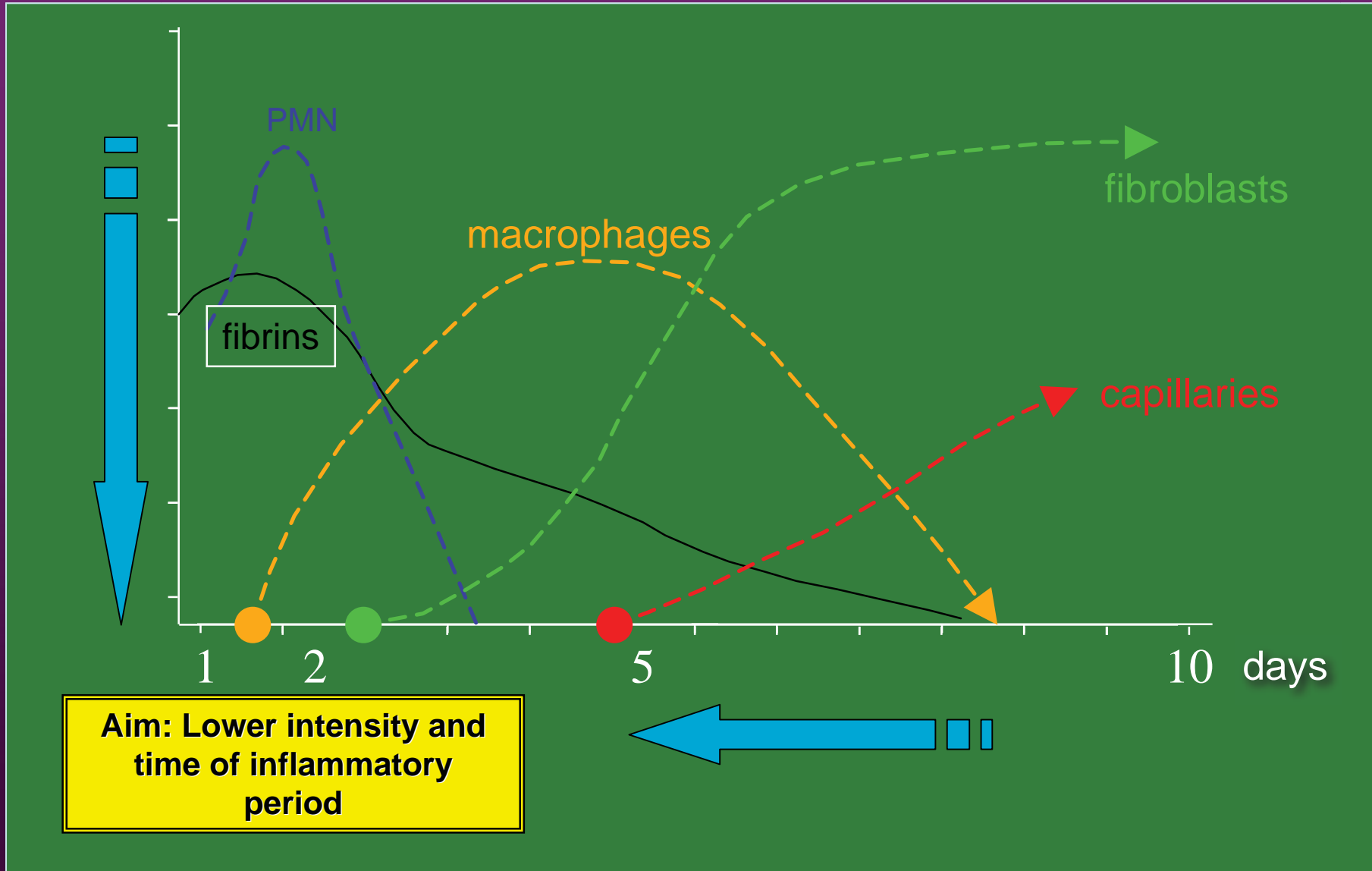
Minimal fibroblast infiltration of the grafts was noted

Only one graft demonstrated new collagen through the entire thickness of the graft limited to a small area

More concerning was an immune reaction in 80% of specimens with lymphocytic infiltrates at the interface of the new collagen and the graft

Histiocytes and multinucleated giant cells engulfing the porcine collagen matrix were present in 2 specimens suggesting a more vigorous foreign body reaction directly to the graft.

Mesh: Growth Into Tissue



Histology of HMDI Porcine Dermis Failure Explants (58 & 67 Weeks)

No remnant of graft was found

***The graft was completely replaced by dense
fibroconnective tissue and moderate
neovascularization without evidence of
inflammation***

**Histology of HMDI Porcine Dermis
Retention Explants (6, 15, 19, 21, & 42 weeks)
Failure Explants (56 & 67 Weeks)**

Conclusion:

HMDI cross-linked porcine dermal implants result in variable tissue reactions that may have unpredictable clinical outcomes in different patients

This variability raises questions about the overall tolerability and efficacy of HMDI cross-linked porcine dermal xenografts in pelvic reconstructive surgery.

Porcine Dermis Sling Failures

*Non-Cross Linked Porcine Dermis Capio CL
Bladder Neck Slings (N=26)*

*Anatomic Failure Measured by Straining Q-tip
Test Angle >30 Degrees at 3 Months Post-op*

Anatomic Failure in 19/26 Subjects

Incidence of Vaginal Extrusion of HMDI Cross-Linked Porcine Dermis

Over 5 Years, 270 Women had Pelvic Slings & Adjuvant Grafts

19 (7%) Partial or Complete Extrusion

Increased Risk after Sling or Diverticulectomy

11/13 After Sling Healed by Reepithelialization & 2 Required Surgery

2/6 Required Surgical Debridement after Adjuvant Grafting

Allografts: Antigenicity

- The risk of transmission of HIV from soft tissue allografts is 1 / 8,000,000.

Buck B, et al: Clin Orthop 251:249-253, 1990.

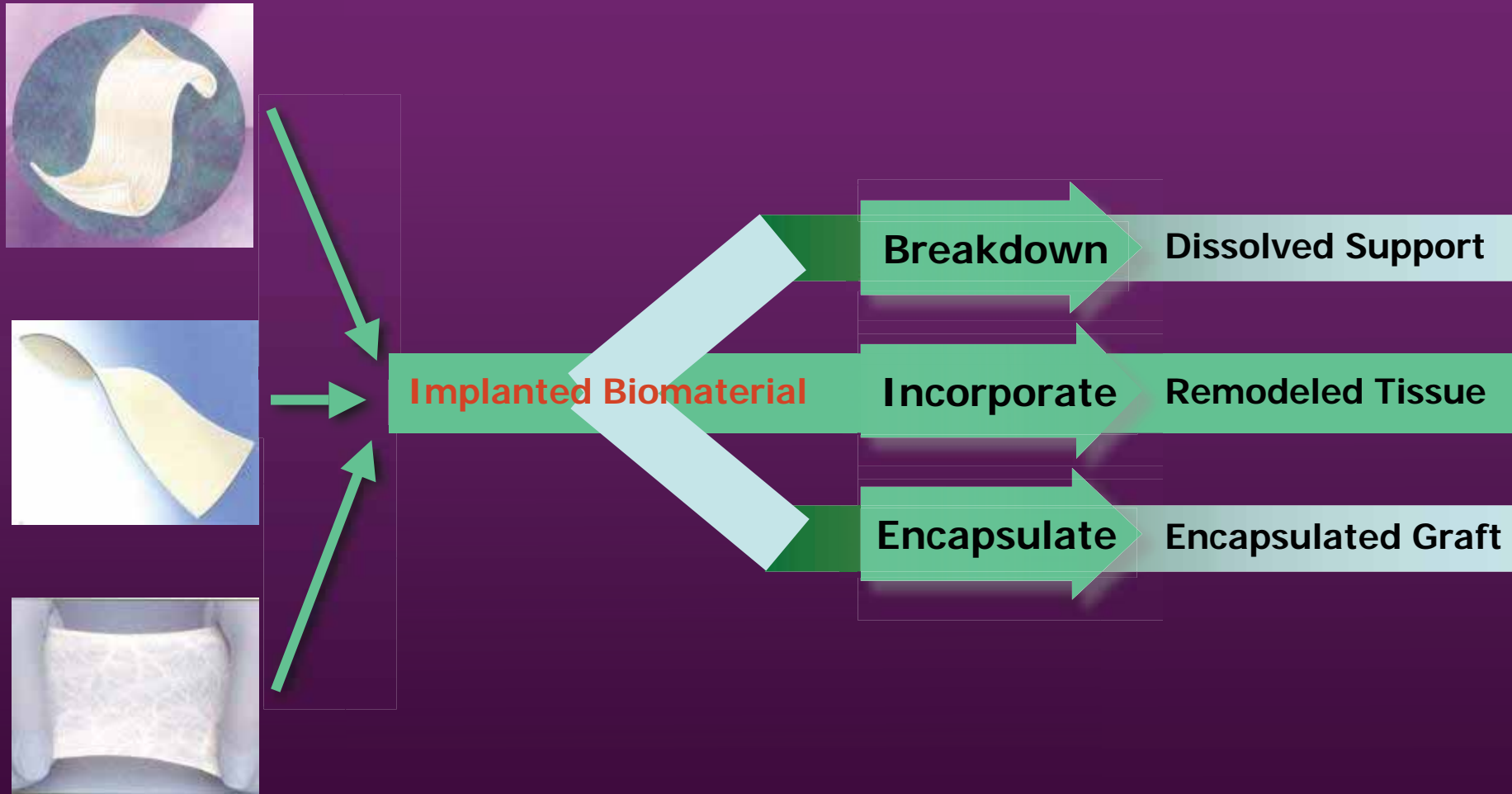
- HIV transmission potential between solid organs and bone is less when compared to soft tissue.

Simonds R, et al: N Engl J Med 326:726-732, 1992.

- Processed tissue retains donor antigens, however after implantation these antigens are replaced by host antigens.

Fitzgerald M, et al: BJU Int 86:826-828, 2000.

In-Vivo Tissue Response of Allografts



DNA Content of Fascia Allografts

- Commercially available fascial allografts contain traces of genetic material.

- *The integrity of the genetic material and potential for amplification are unknown.*

Sadhukhan P, et al: J Urol 161:396(A),1999.

- *FDGI* cadaveric fascia and acellular dermis contains intact DNA.

Choe J, Bell T: J Urol 166:122-124, 2001.

Tissue Degeneration

- Many authors describe the graft material as thinned, or frankly absent upon re-exploration.

Carbone J, et al: J Urol 165:1605-1611.

Fitzgerald M, et al: Am J Obstet Gynecol 181: 1339-1346, 1999.

- This appears to be the most common appearance of the failed allografts.
- Much research is needed to understand what happens to the grafts after transvaginal implantation.

CADAVERIC FASCIA LATA

Anterior Compartment

Kwon, et al (IUGA 2002): 126 Women

Prospective RCT of Fascia Lata Patch

At 1 Year: 3° Cystocele in 13.4%

- 12% No Fascia 1.5% Fascia*

***Regression Analysis: Only Concomitant
Transvaginal Sling Protective (p=0.02)***

*p=0.05

Comparison Studies

Cohort comparison: (non-randomized)

- **Valkili et al** (Am J Obstet Gynecol, 2005): **312 pts, 32%** undergoing graft placement.
 - **No difference in outcome / Higher compl. rate**

Randomized Controlled Comparisons:

- **Gandhi S, et al** (Am J Obstet Gynecol, 2005): **154 pts.** Randomized to graft or no graft.
 - **Solvent dehydrated fascia lata as a barrier does not decrease recurrent prolapse**
 - **Similar findings in 98 patients undergoing posterior repair**

Comparison Studies

Culligan et al (Obstet Gynecol, 2005):

- RCT of Polypropylene Mesh vs. Cadaveric Fasciia Lata for Abdominal Sacrocolpopexy
- Polypropylene Superior to Fascia Lata for Abdominal Sacrocolpopexy.

NICE: National Institute for Health and Clinical Excellence

Too few data for most outcomes

May be some evidence of objective efficacy, but this must be considered along with safety concerns.

For all prolapse types, there was not enough information to compare any of the other efficacy outcomes or other safety outcomes.

“Absence of Proof may not be Proof of Absence”

EVIDENCE LACKING

2008 Evidence Based Review by Society of Gynecologic Surgeons Systematic Review Group

75/2260 articles

- 17 comparative studies (7 RCTs)
- 58 non-comparative or case reports

Data from RCTs is not sufficient to recommend graft use in vaginal POP surgery.

Conclusion

Good Reports in the Literature are Conflicting and not Consistent with Histiological Data

First Generation Biomesh is not Optimal as an Adjuvant Graft for Improving Long-term Surgical Success of Reconstructive Operations