Biomaterials in the development of vascular grafts

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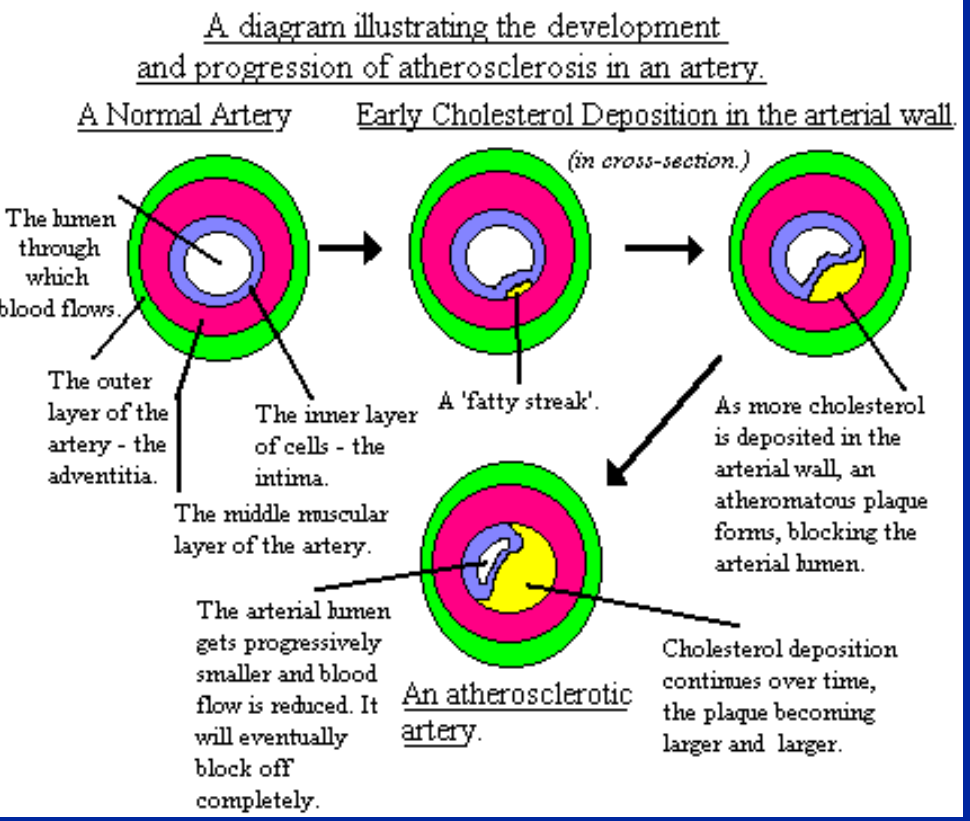
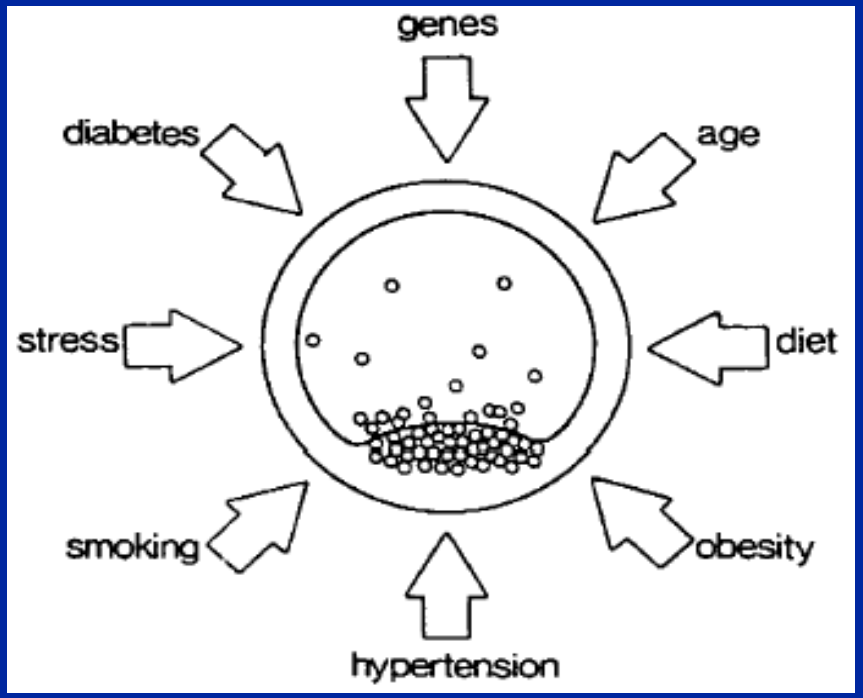
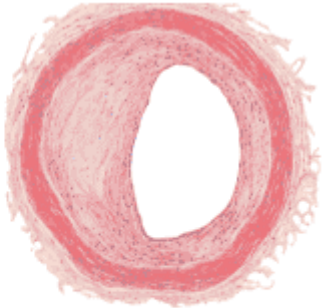
Importance of arterial diseases

- Most common causes of morbidity and mortality in peoples of middle age and older
- Arterial diseases belong to two group:
  - Degenerative (arterosclerosis – largely diffused)
  - Inflammatory (arteritis - numerically uncommon)
- Arterosclerosis is usuallyconsidered to be concomitant of aging
- Arterial occlusion causes more than 500.000 death in North America each year

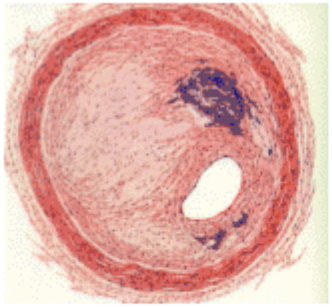




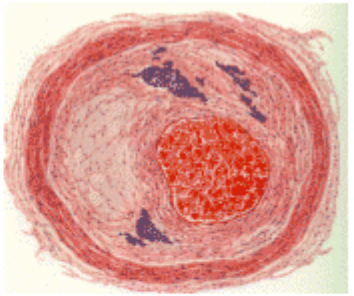
Normal Arterial Lumen



Moderate Atherosclerotic Narrowing of Arterial Lumen



Almost Complete Occlusion of Arterial Lumen by Intimal Atherosclerosis with Calcium Deposition



Complete Occlusion by Thrombus in Arterial Lumen

Possible surgical treatment of arterial diseases

1. Repair the diseased artery if possible
2. Reopen an occluded or narrowed artery by endarterectomy
3. Reopen an occluded or narrowed artery by balloon dilatation and/or stenting
4. Develop or promote collateral circulation
5. Replace or by-pass the occluded or narrowed artery with an arterial substitute (biological or synthetic)

The ideal arterial graft

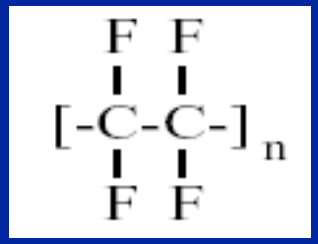
1. Durability superior to life expectancy of the host
2. Not cause undesirable reactions
3. Nonthrombogenic surface
4. Patency should approach 100%
5. Compliance and flexibility as the natural artery
6. Integration with surrounding tissue
7. Readily sterilizable with standard methods
8. Readily available in a variety of sizes and lengths
9. Easy to handle for the surgeon
10. Inexpensive as much as possible

Current synthetic arterial grafts

- Only PTFE and PET are currently used
- Materials, such as Nylon, Orlon, Ivalon have been used but now belong to history
- Other materials under investigation might become important in the near future, especially Polyurethanes (PU) and Polydimethylsiloxane (PDMS) (Silicone)

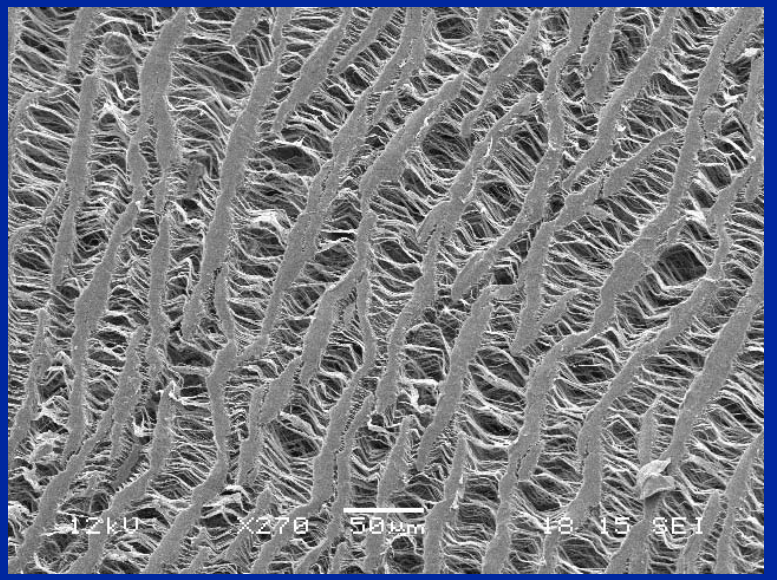
PTFE Grafts

- Polytetrafluoroethylene (PTFE), also known as Teflon®



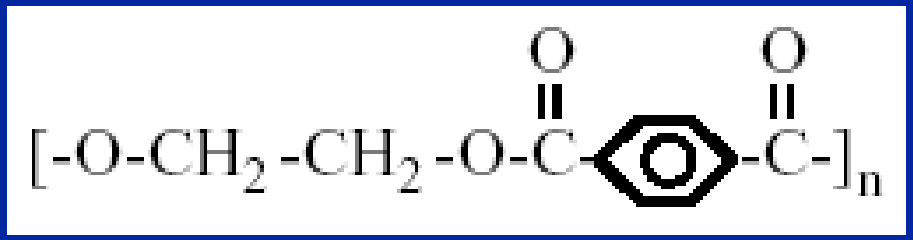
Example of commercial PTFE

Expanded PTFE



PET Grafts

- Poly (ethylene terephthalate) (PET), also known as Dacron®



Bifurcated- crimped

Straight-crimped

Woven PET

Knitted PET

Main problem of current synthetic arterial grafts

- PTFE and PET grafts are rather successful for the replacement of large diameter, high-flow arteries
- By-passes of long segments of arteries with less than 6 mm ID show poor long-term patency
- To date no synthetic is available as small-diameter graft
- Thrombogenicity of the luminal surface remain the main problem

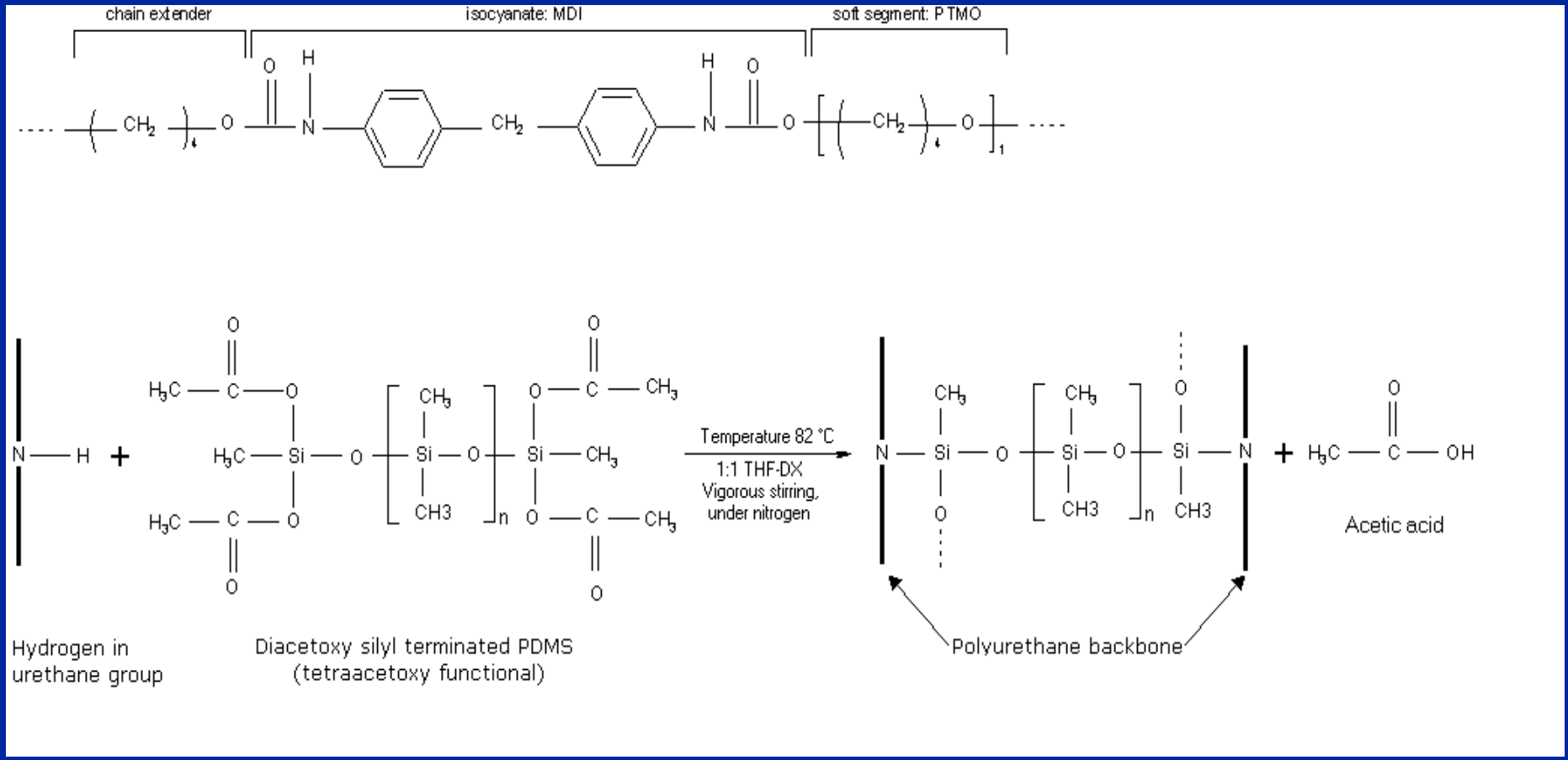
Other general problems of current synthetic arterial grafts

- Compliance mismatch
- Lack of flexibility
- Graft infections
- Insufficent durability

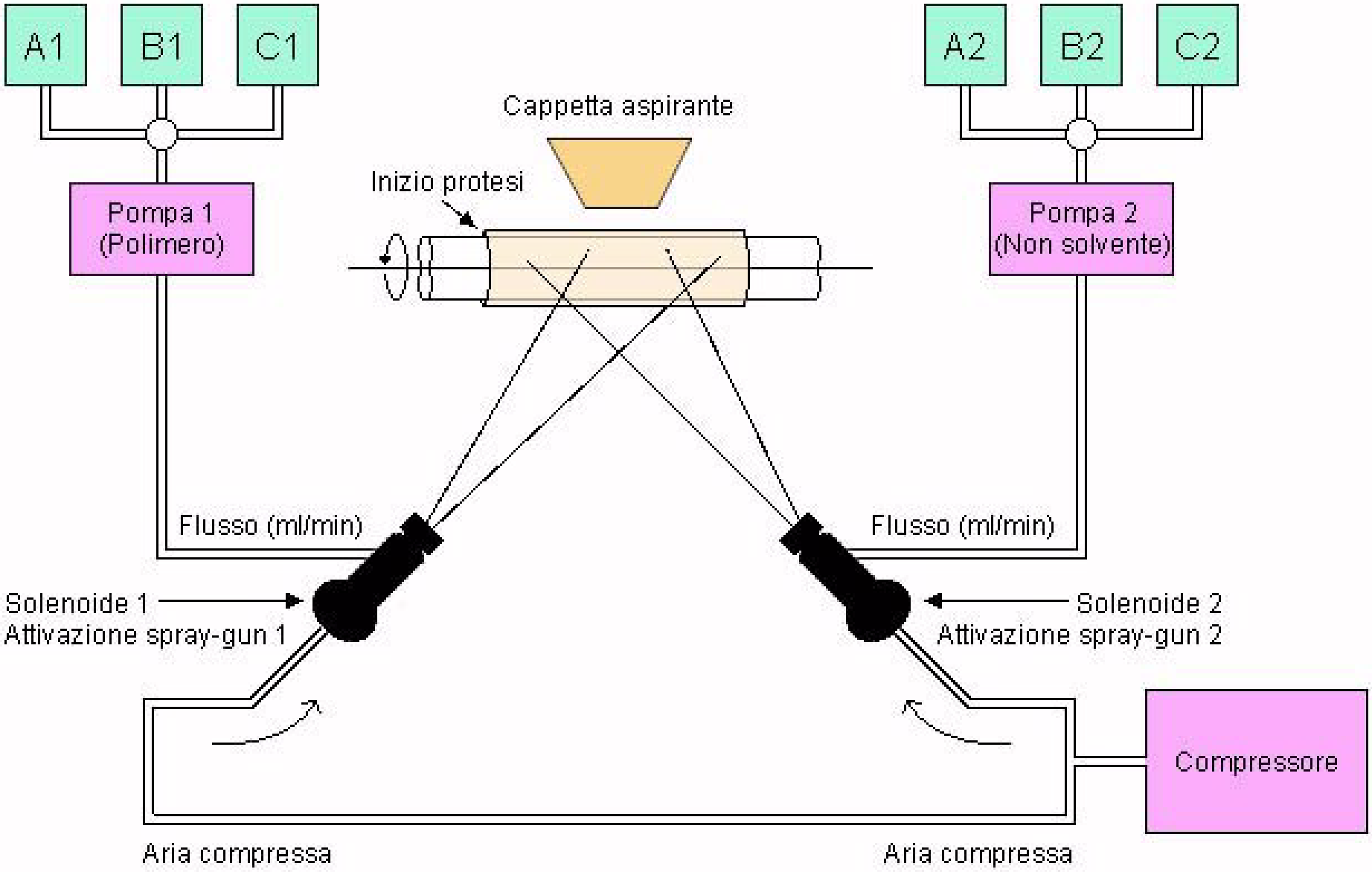
Alternative elstomeric graft materials

- Elastomeric polymers offer a good opportunity to match the elastic properties of natural arteries
- Polyurethane (PU) elastomers are synthetized from an aliphatic diol, the "soft segment" and a methylene diphenyl-diisocyanate and chain extender to form the "hard segment"
- They can be easily modified by changing the ratio between hard and soft segments
- PU elastomers have excellent biocompatibility and mechanical properties
- Polydimethylsiloxane (PDMS) elastomers (silicone) have shown excellent blood compatibility and biostability in long-term implants

Polyurethane (PU) - Silicone (PDMS) reaction mechanism

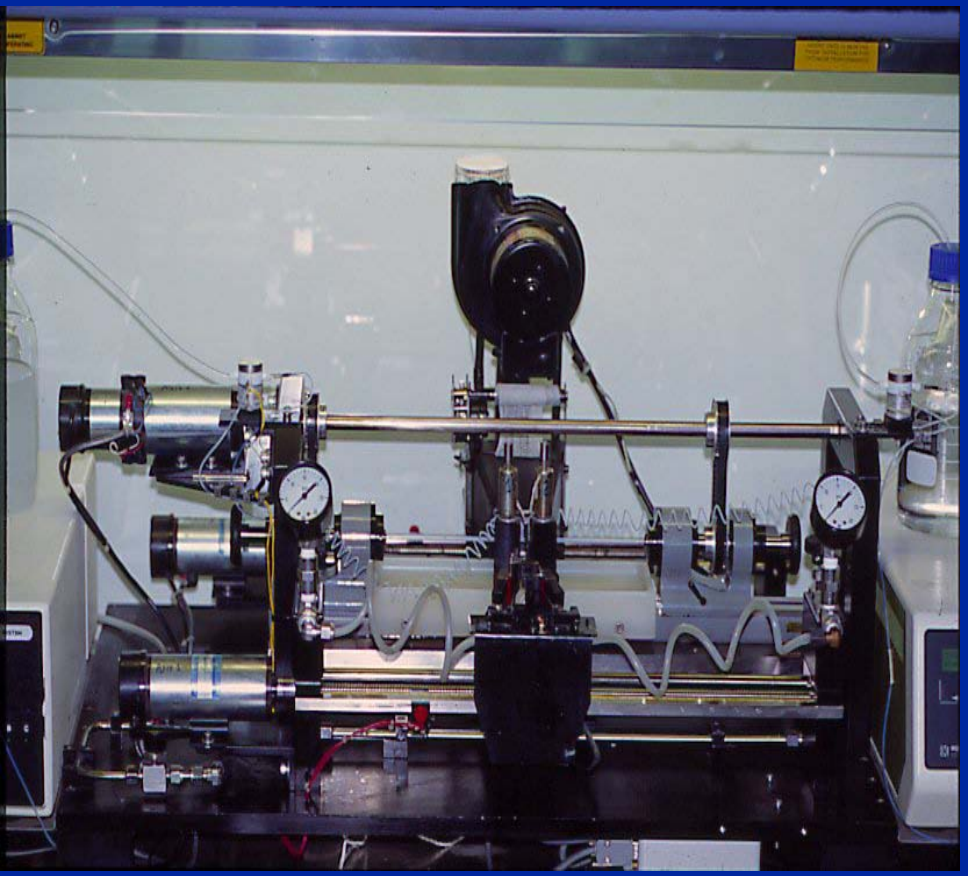


Material processing - “Spray, phase-inversion process”

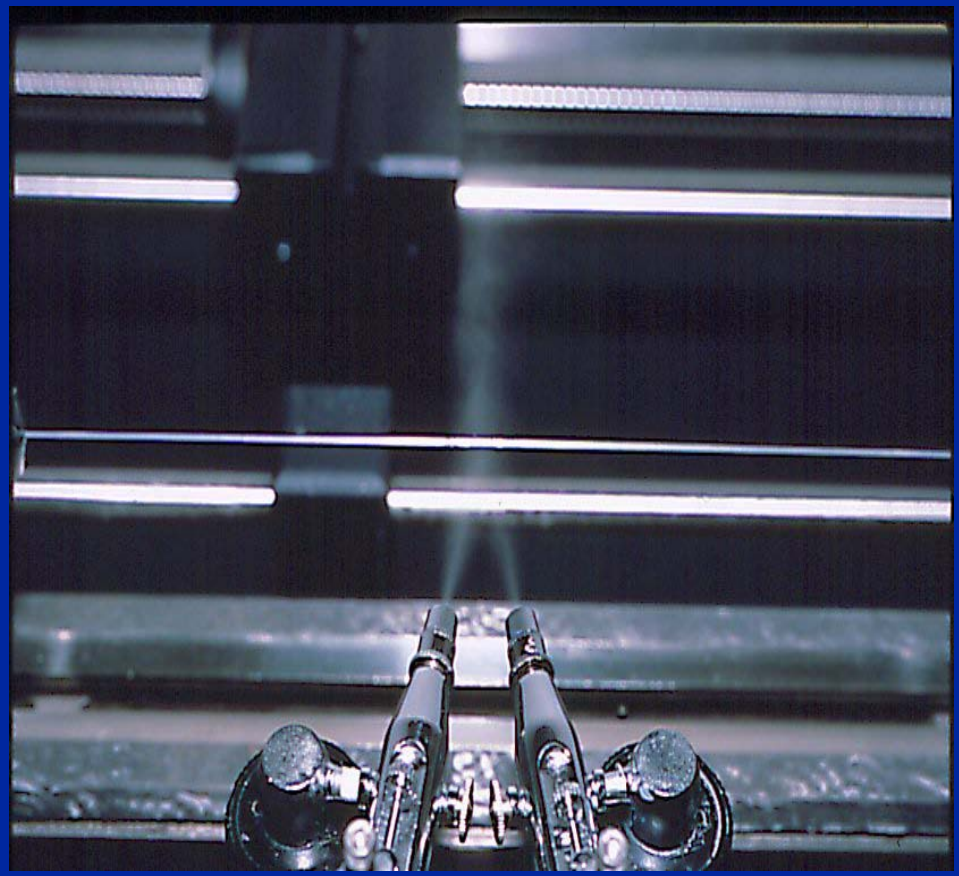


Grafts fabrication

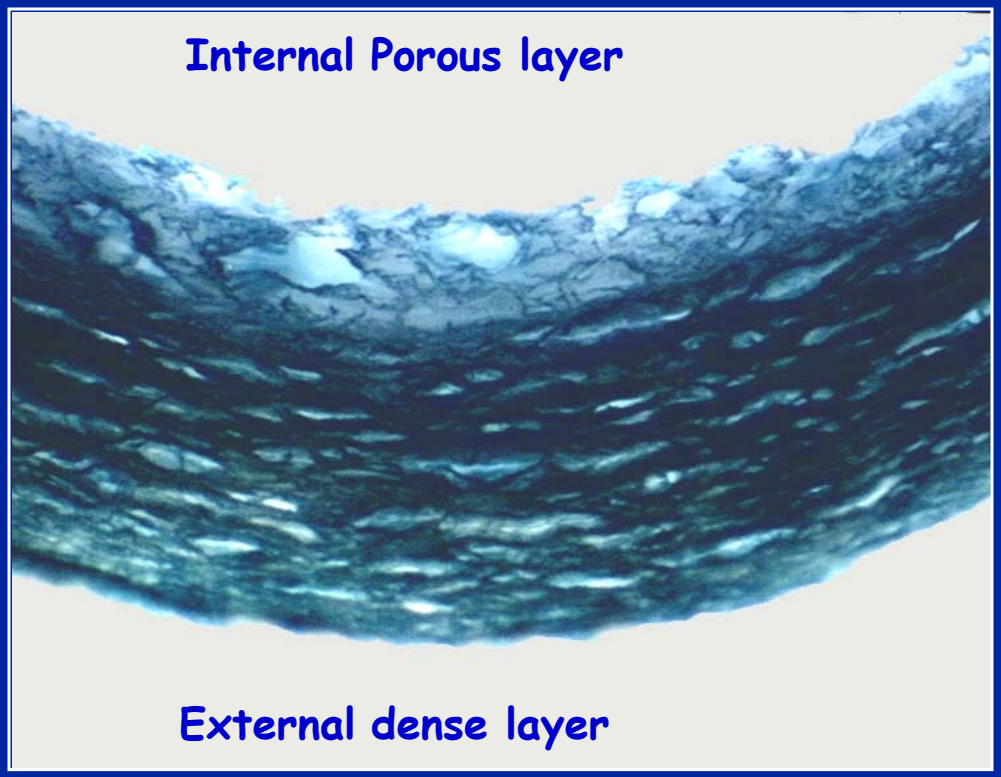
"Spray-machine"

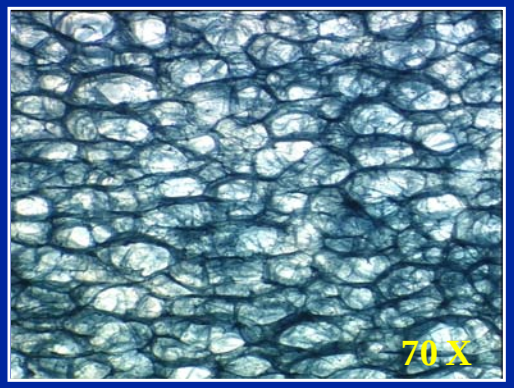


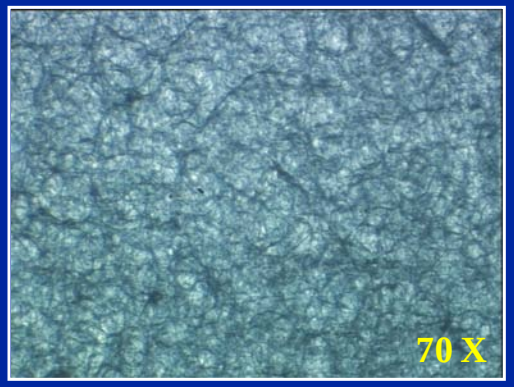
Detail of the spray-guns



Structure of a "pilot graft" PU/PDMS SDVG







Graft luminal surface image analysis

Pores size measurement

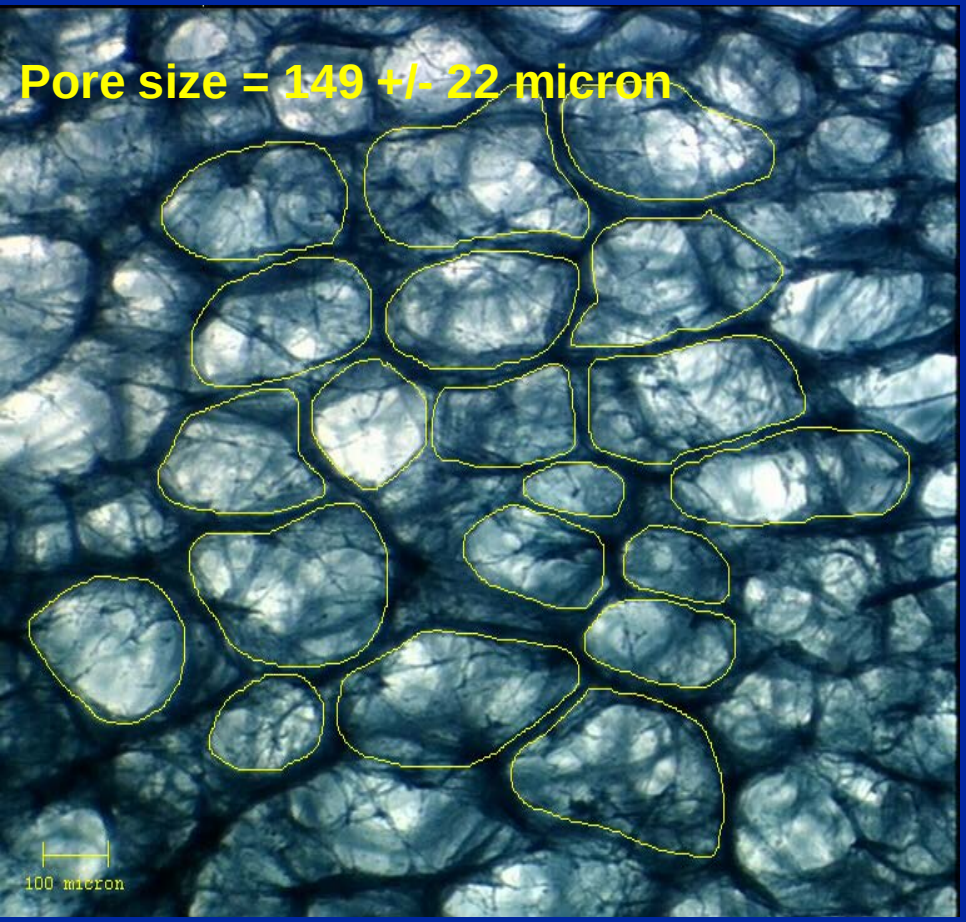
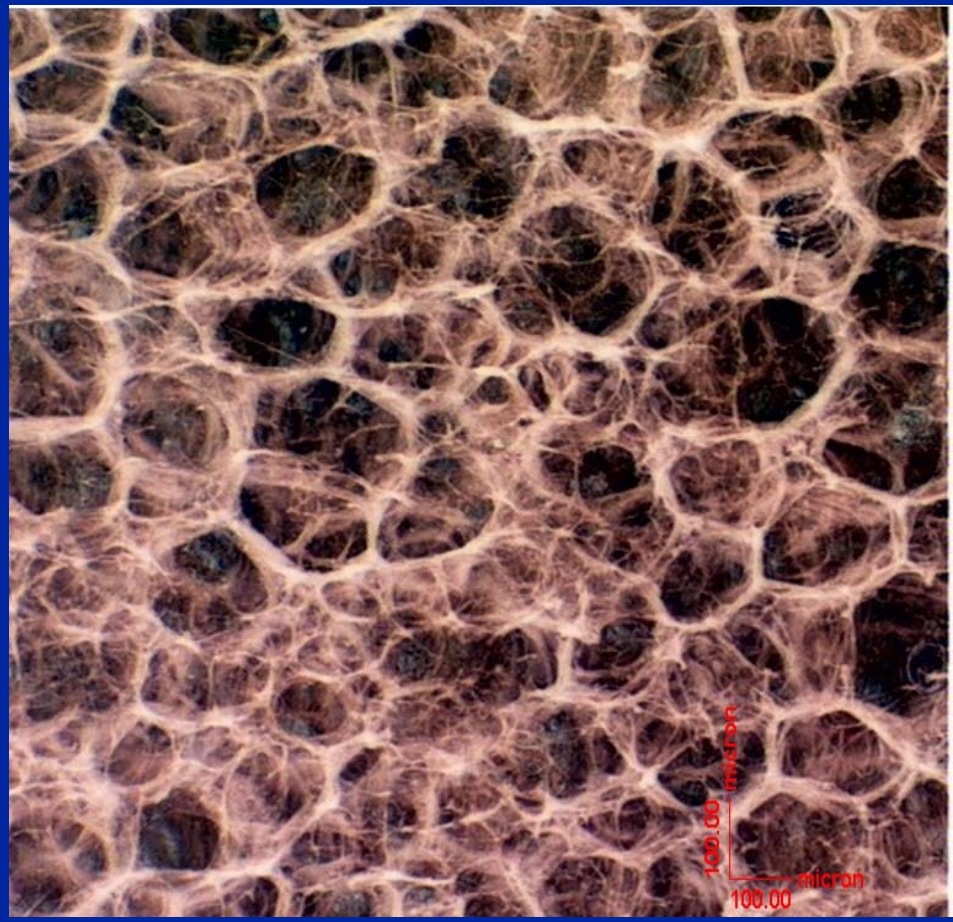
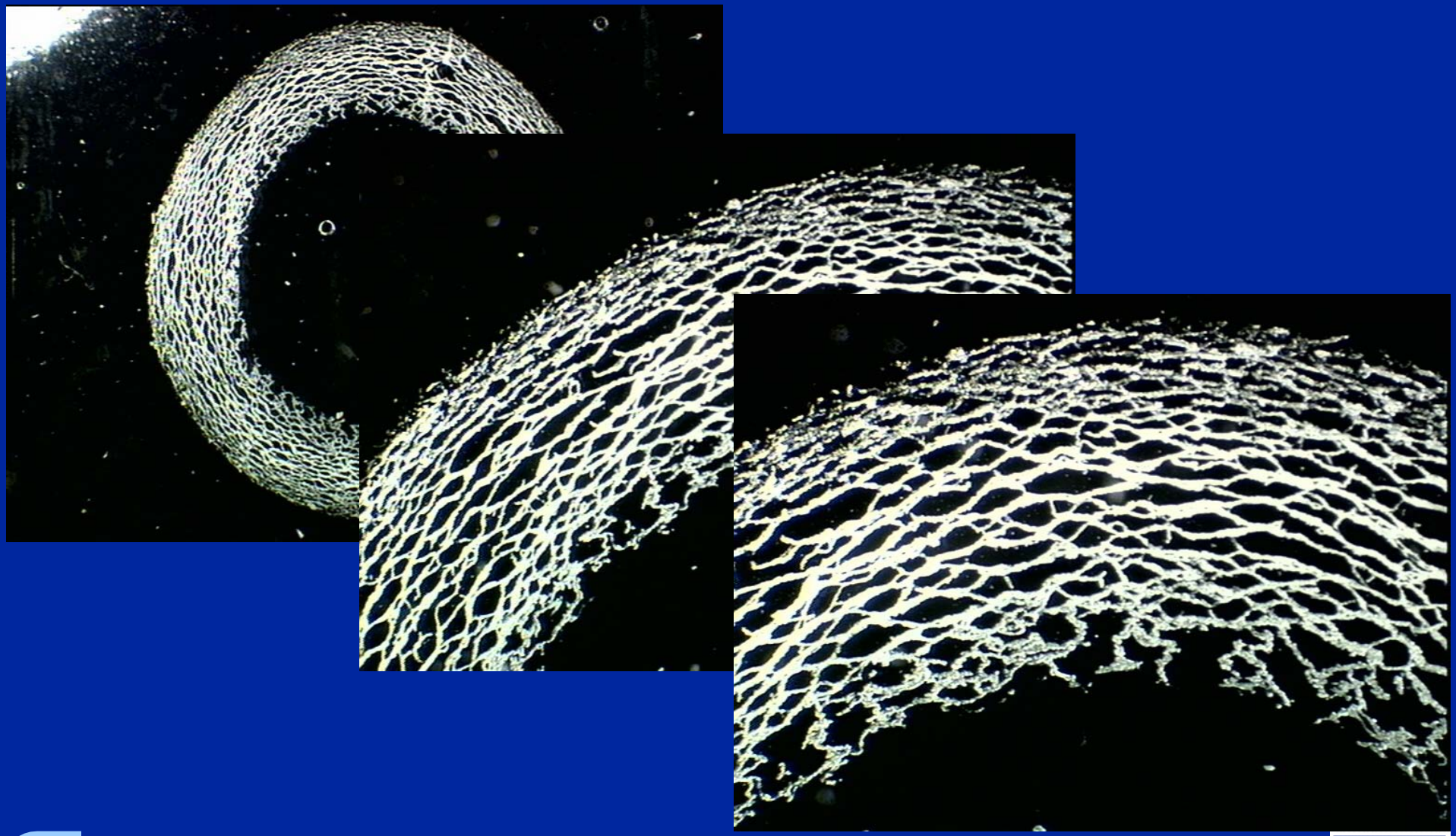


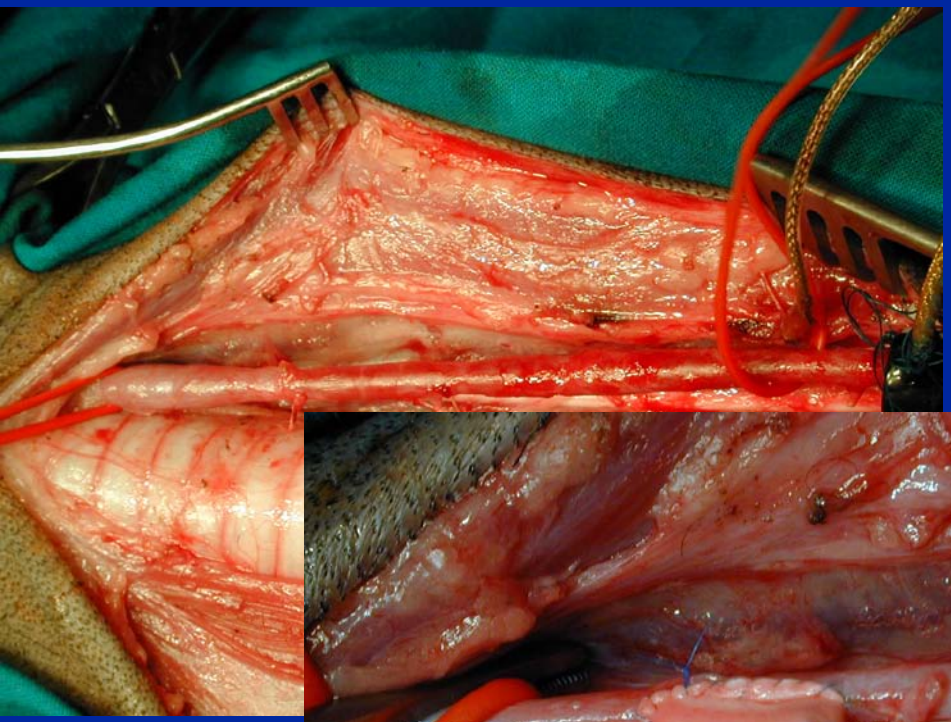
Image with inverted colour

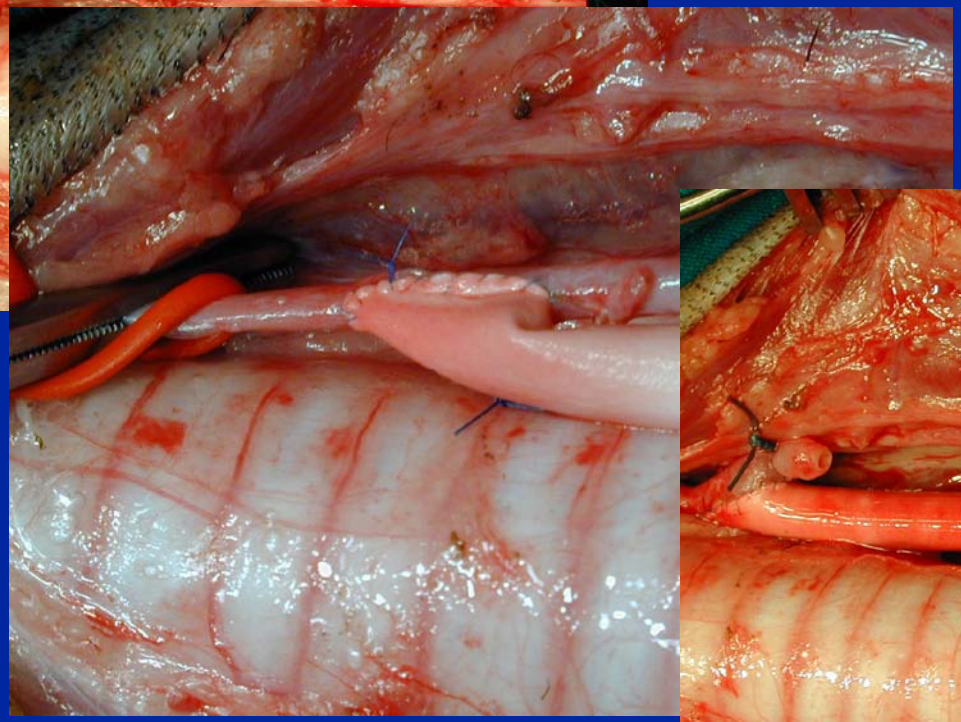


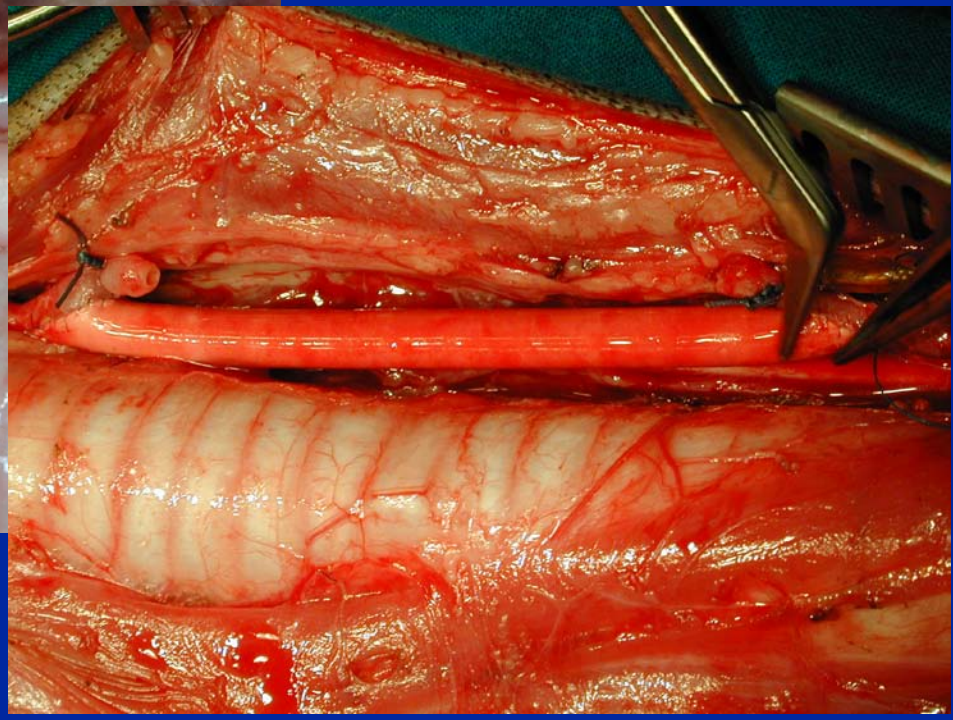
Lifgt microscopy of a graft cross-section obtained by the cryostate

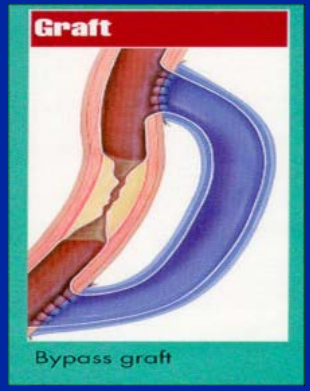


Steps of a graft implant in the by-pass carotid sheep model

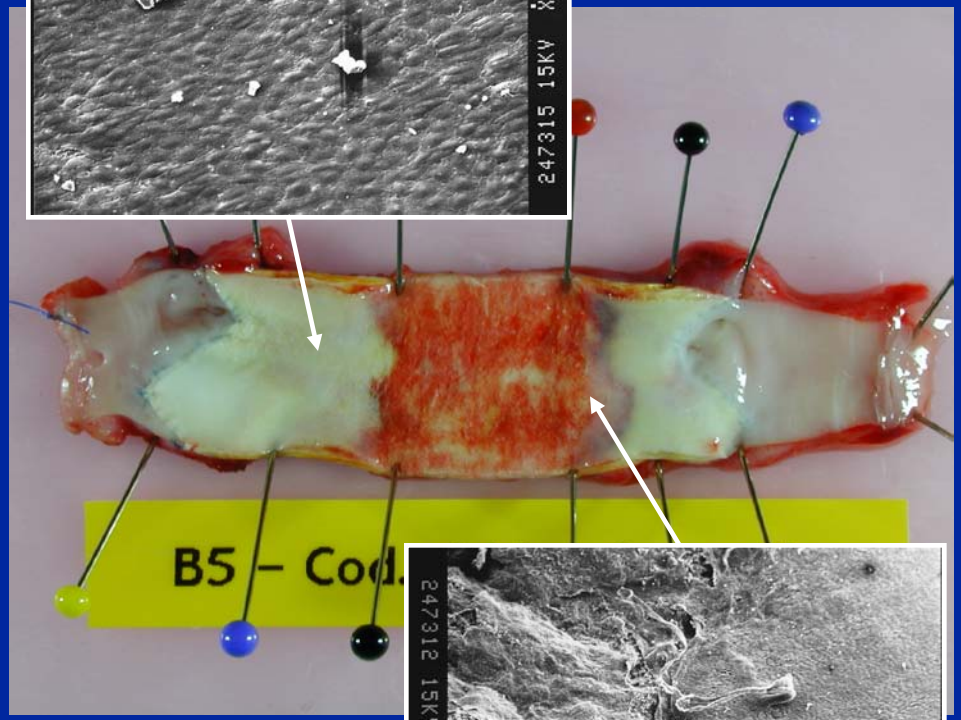


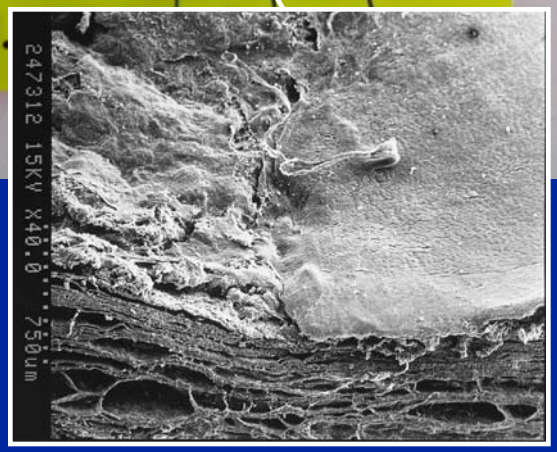


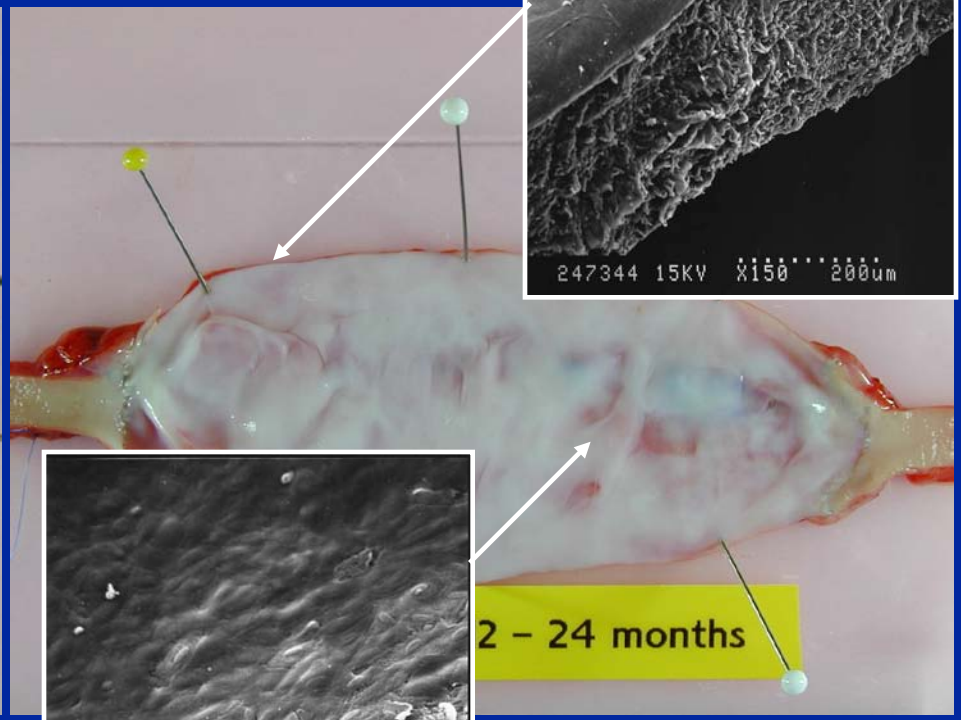




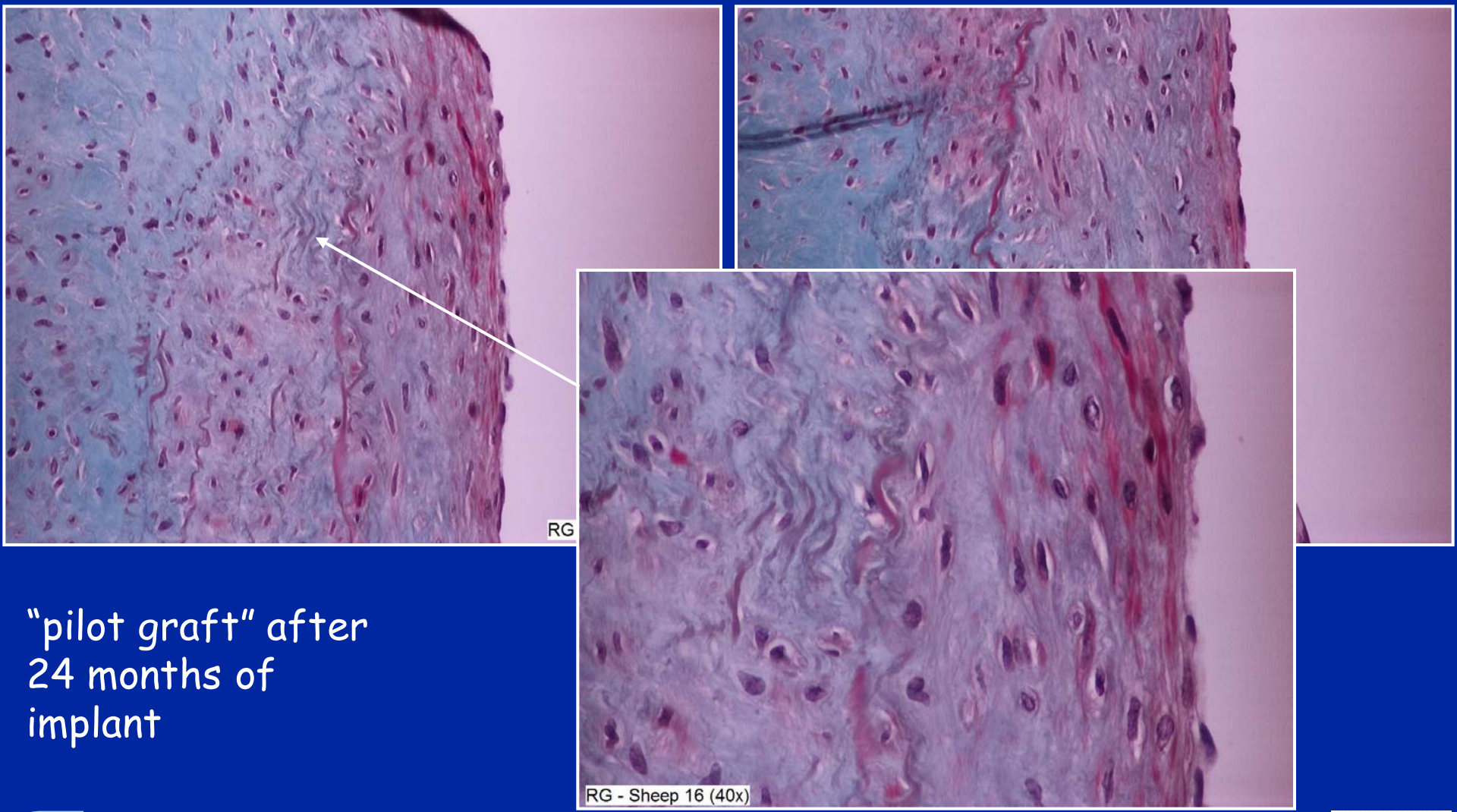
Pilot grafts explanted at 6 and 24 months



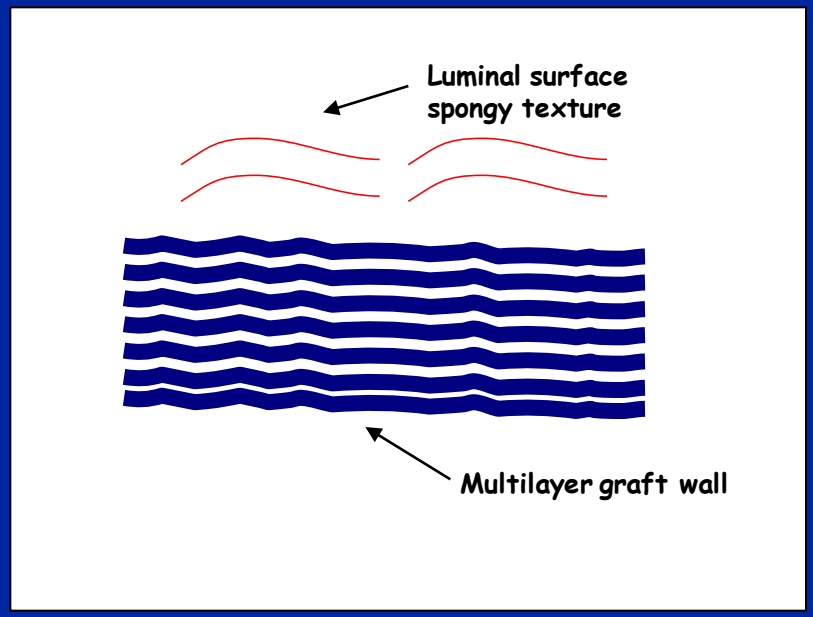




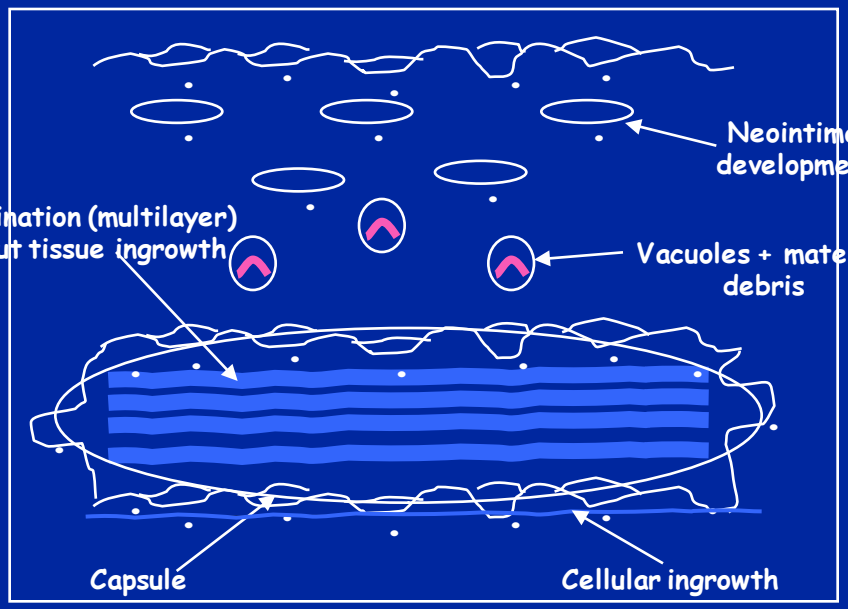
Endothelial cells, smooth muscle cells and signs of elastogenesis ?



"pilot graft" after 24 months of implant

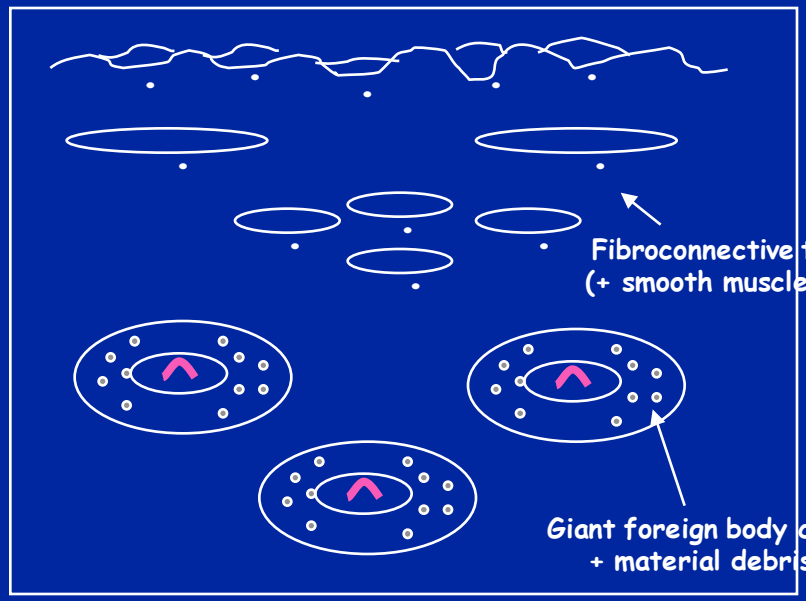


At time of implantation



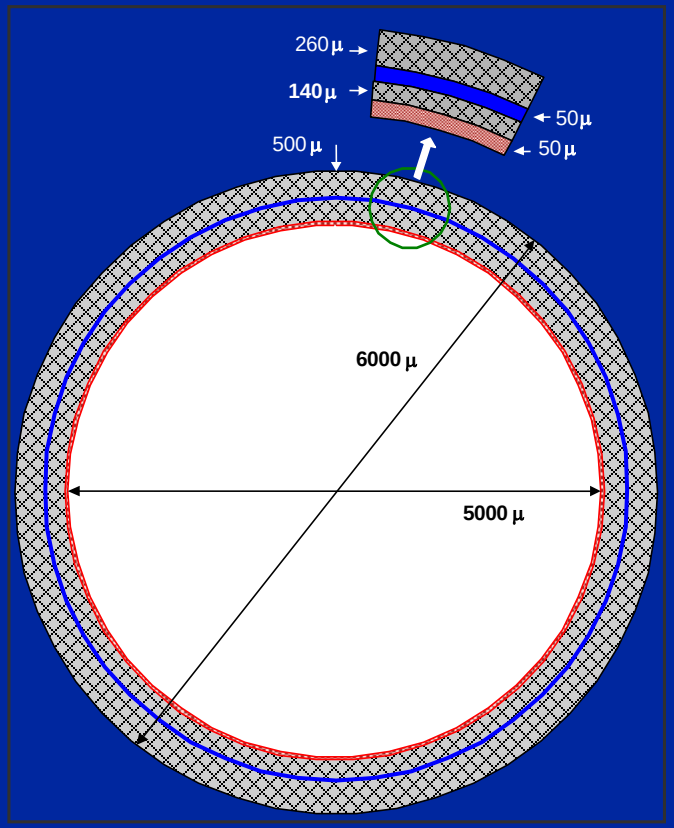
After 5 to 9 months

Schematic diagram of graft biodegradation and tissue replacement

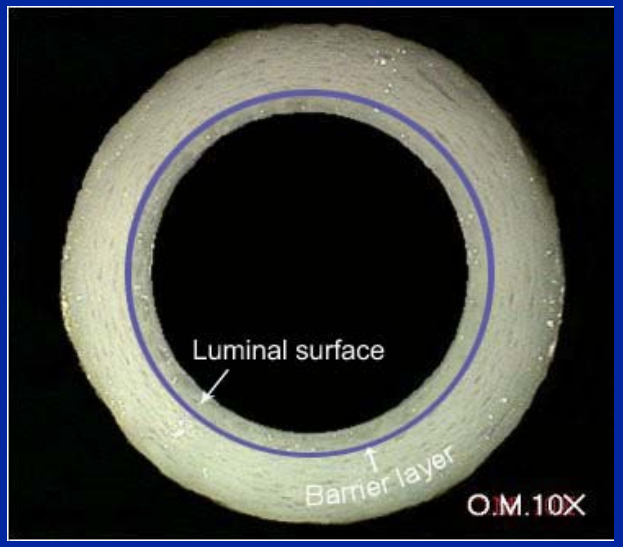


After 24 months

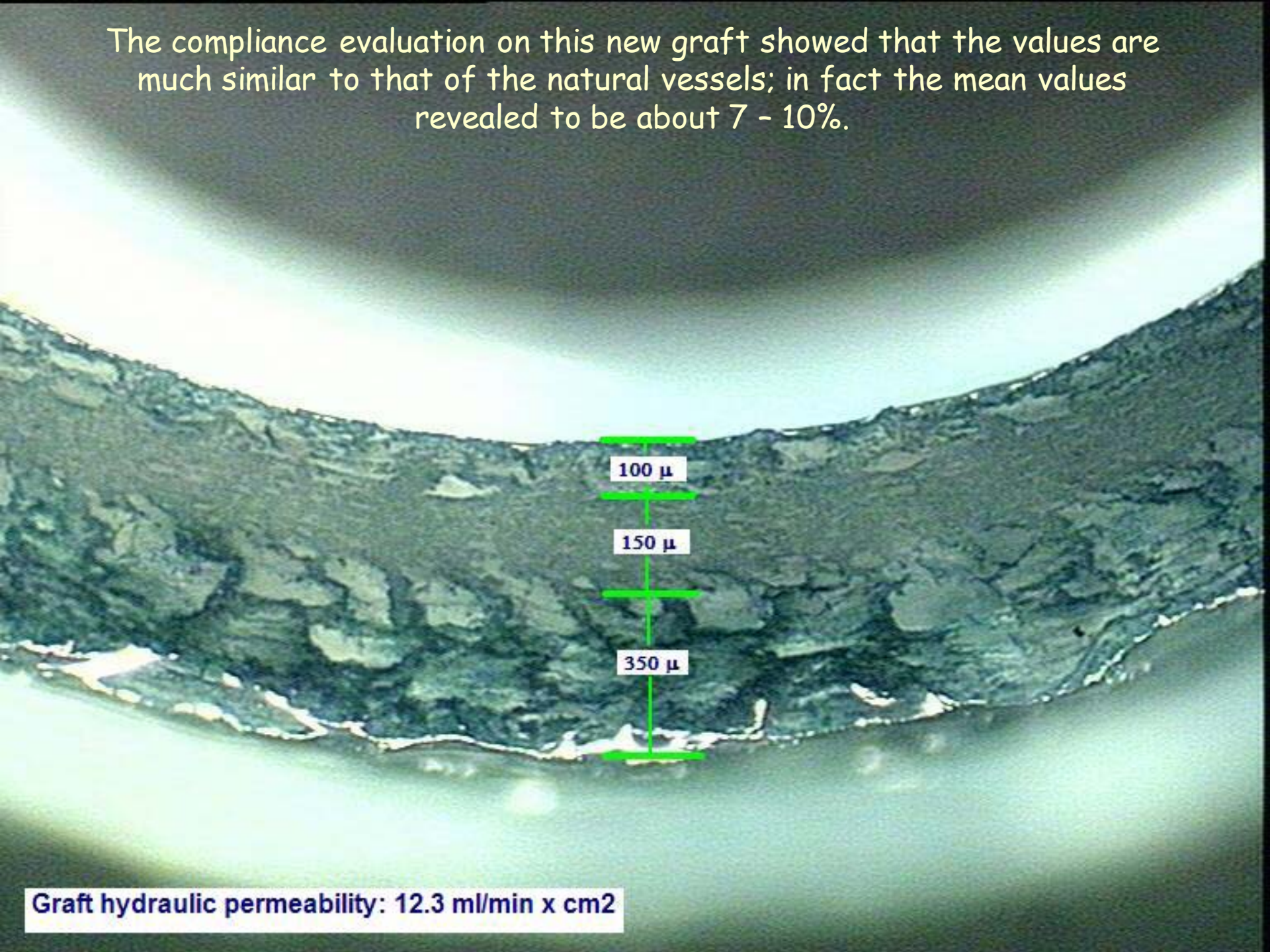
To mimic natural artery compliance – introduction of a low porosity dense layer in the graft wall



Schematic representation of the graft wall with different layers



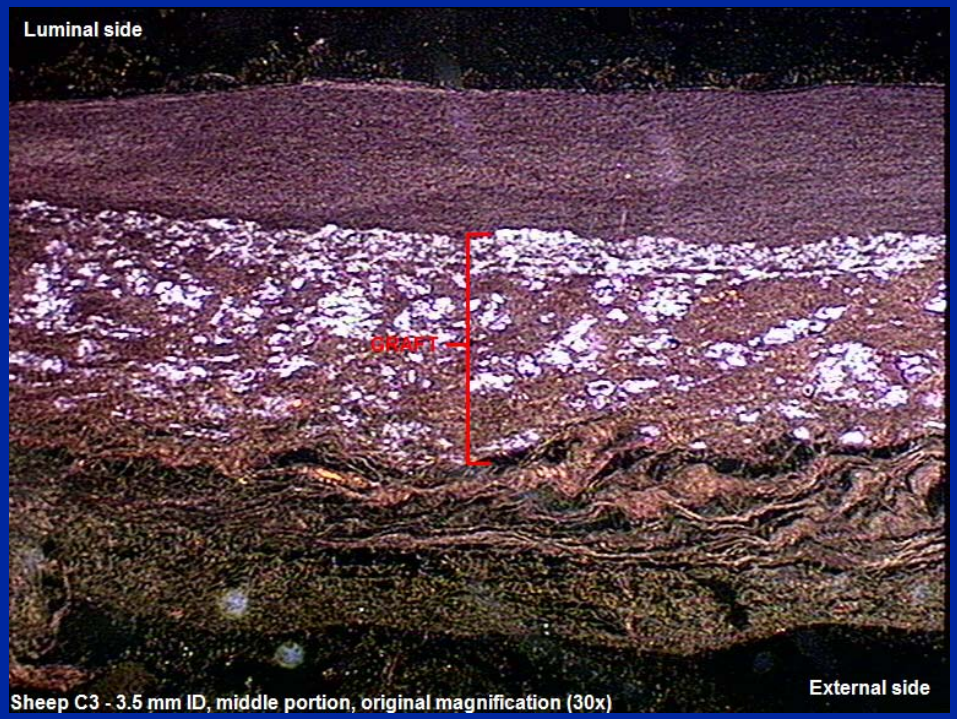
The compliance evaluation on this new graft showed that the values are much similar to that of the natural vessels; in fact the mean values revealed to be about 7 – 10%.



Graft hydraulic permeability: 12.3 ml/min x cm2

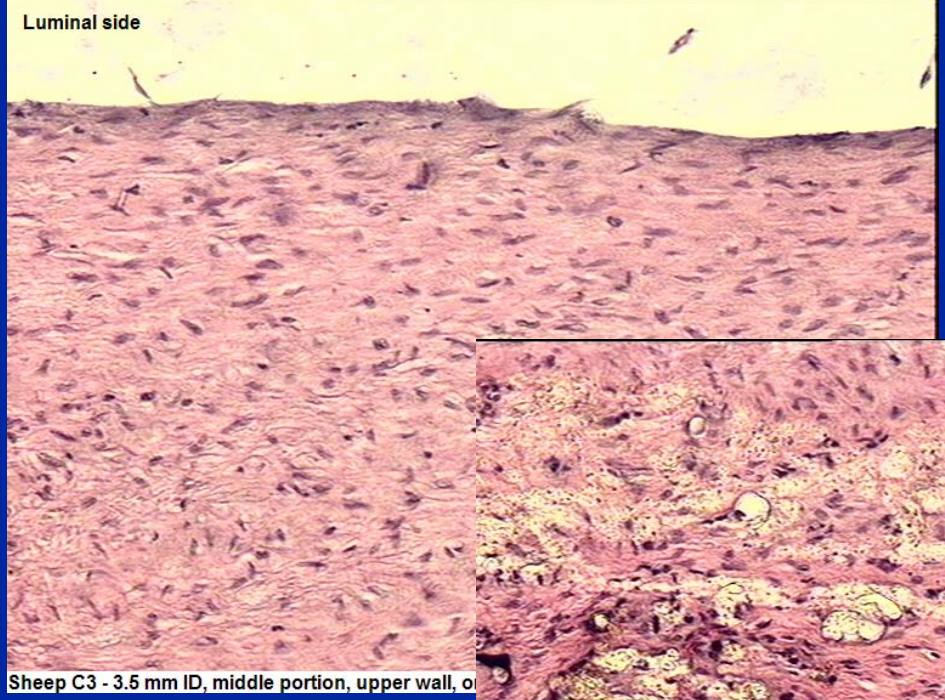
Longitudinal section of a graft with a low porosity dense layer in the wall - after 4 months implant

H & E – Brightfield (30X)



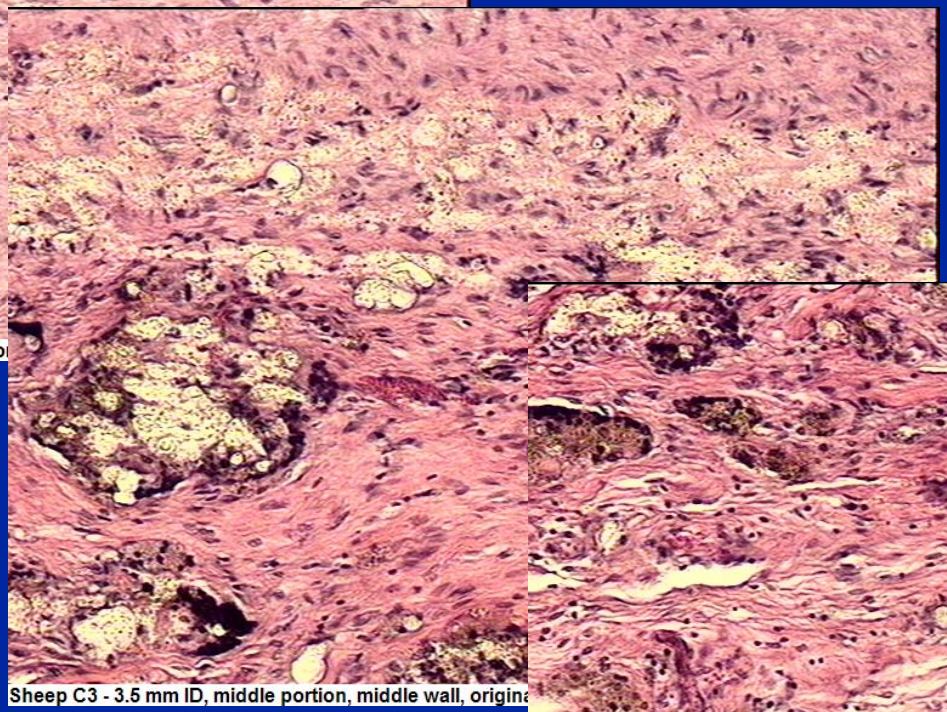
H & E – Darkfield (30x)

Tissue ingrowth and integration in the graft wall

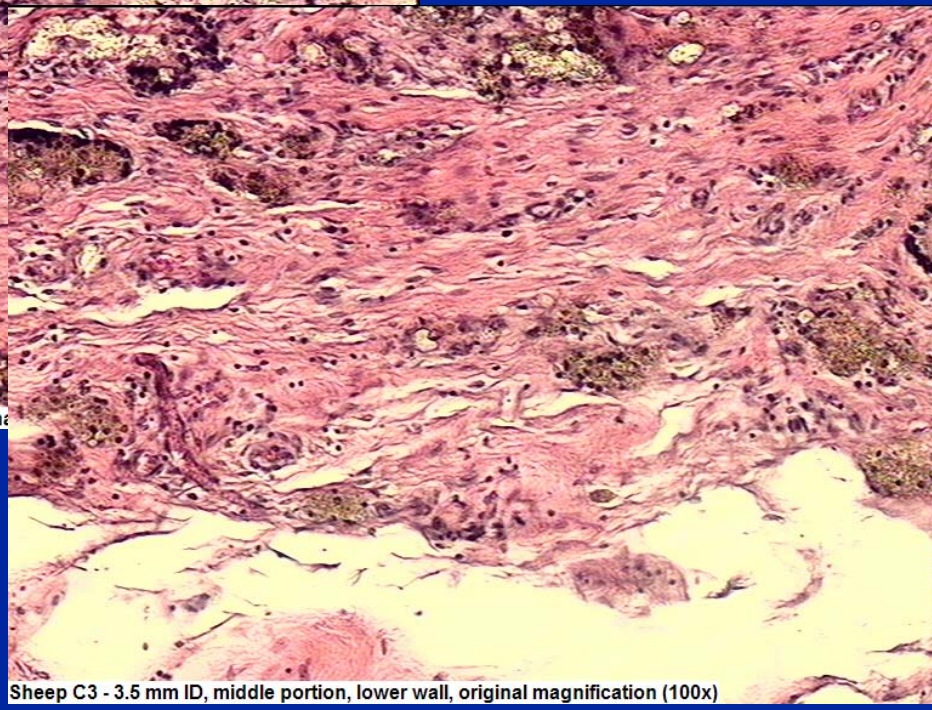


Sheep C3 - 3.5 mm ID, middle portion, upper wall, o

Upper part of the graft wall

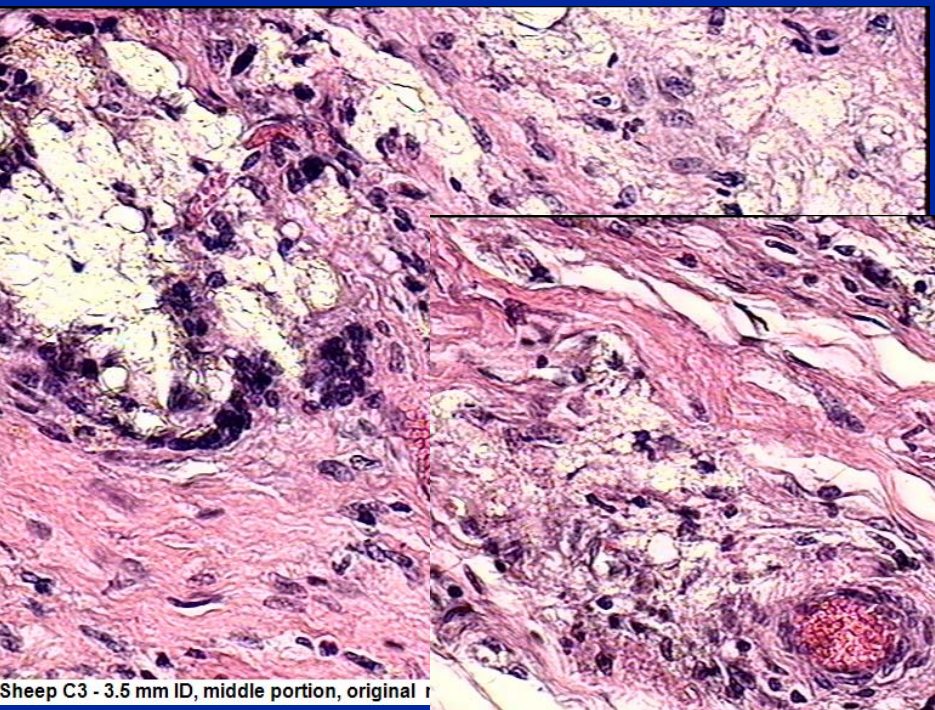

Sheep C3 - 3.5 mm ID, middle portion, middle wall, origin

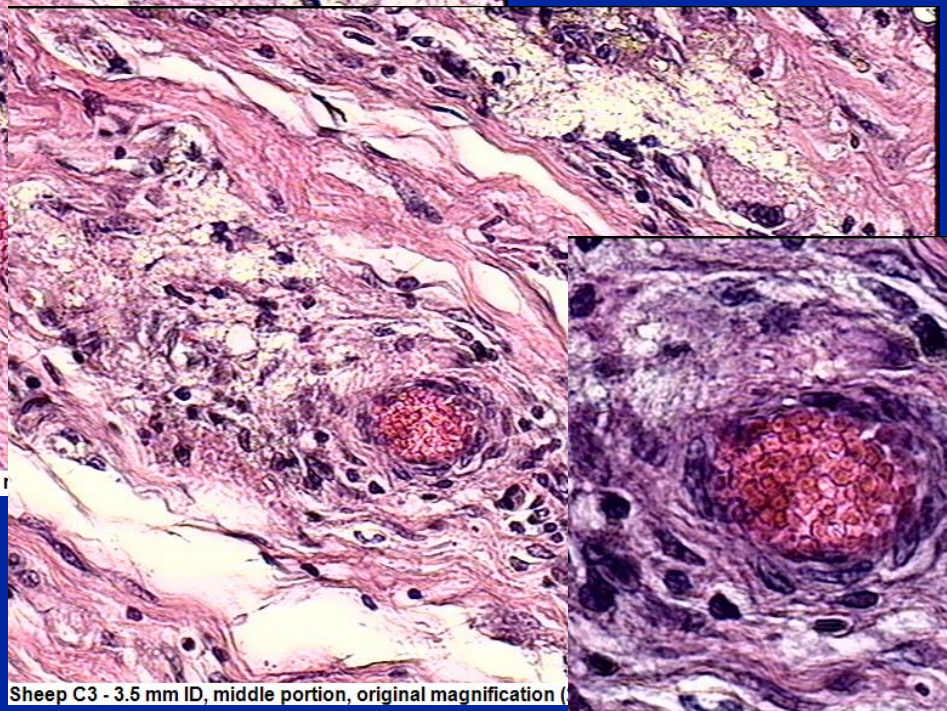
Middle part of the graft wall

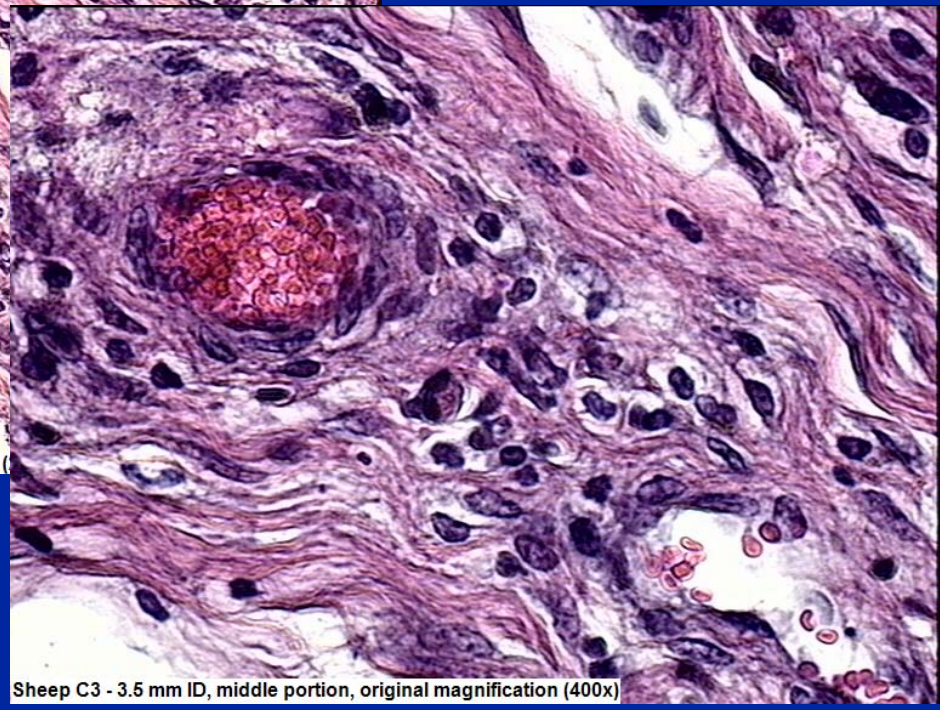

Sheep C3 - 3.5 mm ID, middle portion, lower wall, original magnification (100x)

Lower part of the graft wall

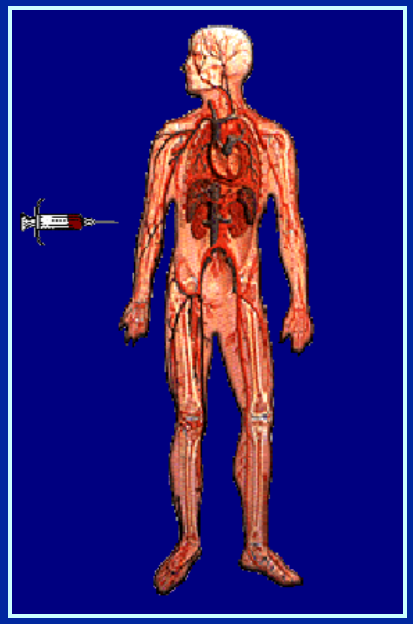
Capillary ingrowth in the graft wall







Prospects for the Future



Human plasma

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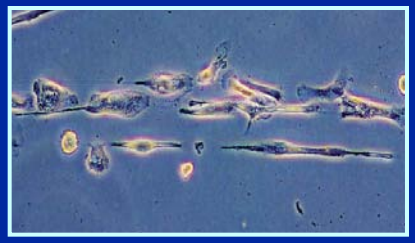

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Microporous vascular graft

CD34⁺ hematopoietic progenitor cells derived from the peripheral blood and differentiated into endothelial cells *in vitro*

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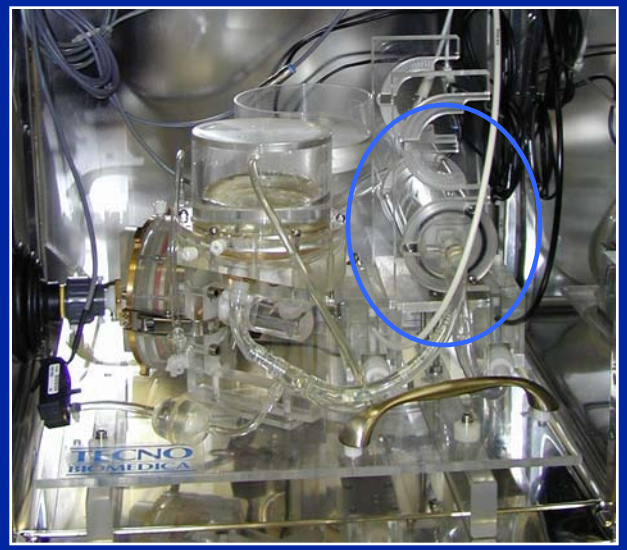
Endothelialisation of synthetic vascular graft

Synthetic vascular graft

+

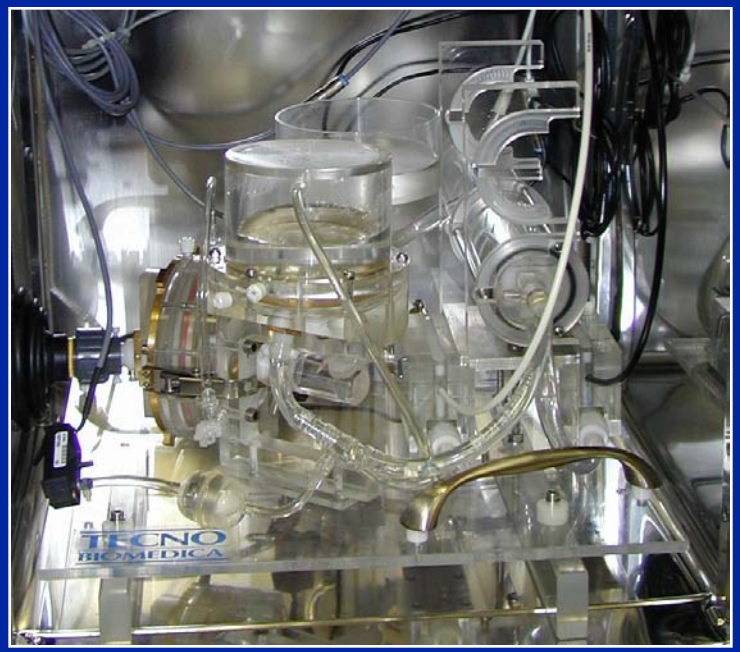
CD34⁺ progenitor endothelial cells

Colture chamber



Bioreactor

Endothelialisation of synthetic vascular graft



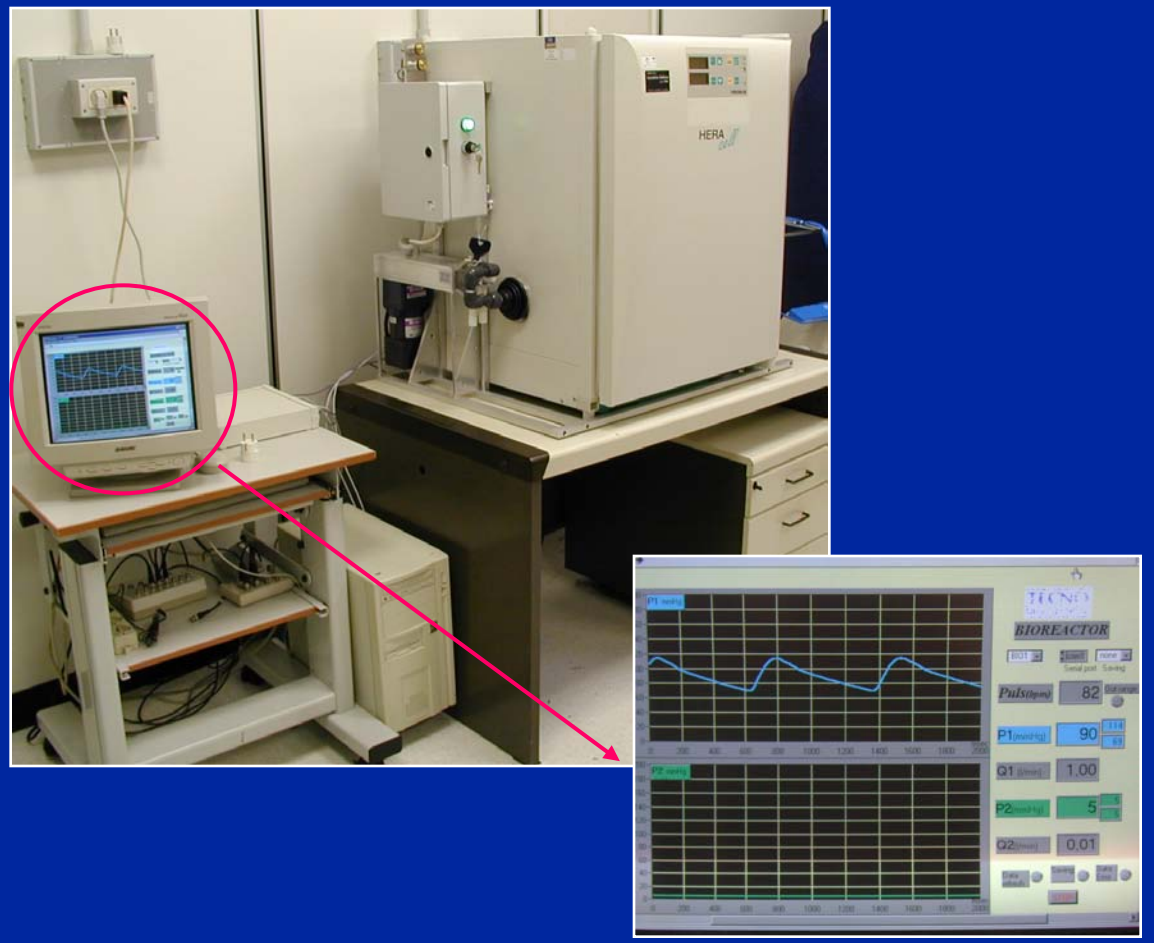
Bioreactor

Bioreactor located into a standard CO_2 incubator

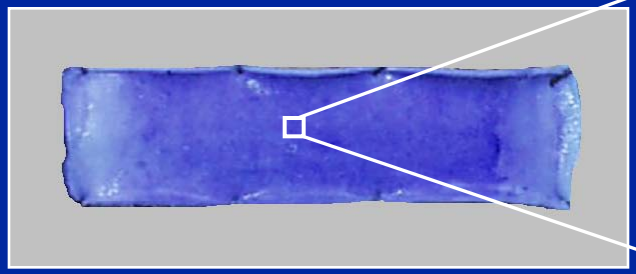
Endothelialisation of synthetic vascular graft

Controlled parameters:

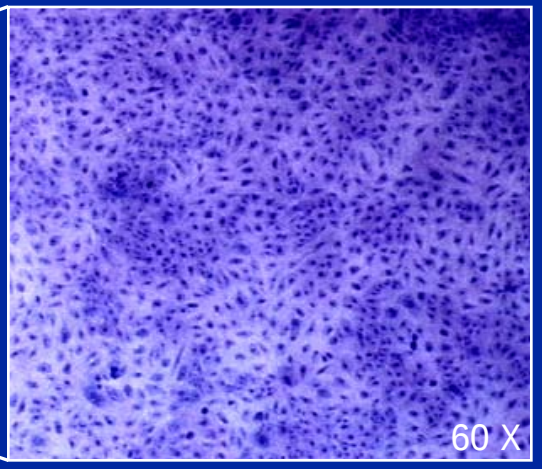
- Aortic waveform
- Pulse pressure (ΔP)
- Average pressure (0-200 mmHg)
- Flow (0-1000 ml/min)
- CO_2 (5%)
- Temperature (37°C)



Results obtained up to now



Fibrin coated vascular graft after endothelial cells seeding and incubation for 24 hours in the bioreactor



Microscopical observation after staining of cells with Giemsa solution (0.1% in methanol)

Important note: a complete coverage of the luminal surface with the endothelial cells was obtained after only 24 hours of incubation in the bioreactor colture chamber

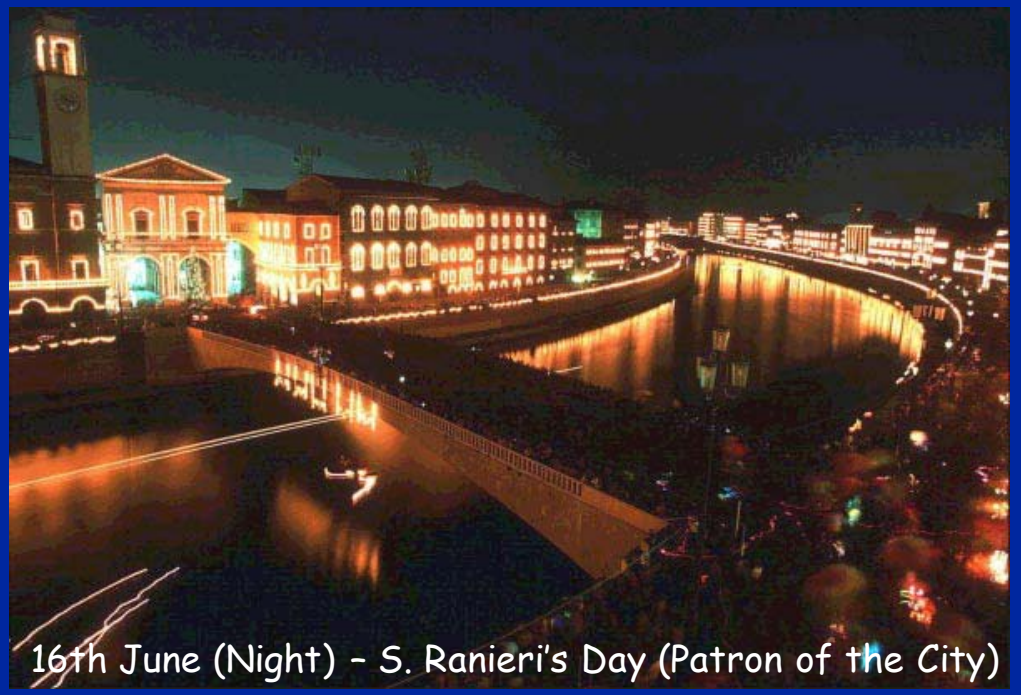
Conclusions

- The PU/PDMS graft material under development appears to be a slow degradable scaffold starting its degradation at about 5-6 months
- The degradation/inlfammation process associated is very mild and do not inhibit the occurrence of a true vascular differentiation at the scaffold site (capillary formation and smooth-muscle cell differentiation)
- The PU)/PDMS graft material can be employed as a bioresobable scaffold for tissue engineering applications
- The capability of modulating graft material degradation in exchange of tissue and capillary ingrowth will be a major challenge for next graft generation

Acknowledgments

Team involved in the research work:

- Dott. Paola Losi
- Dott. Enrica Briganti
- Mrs Ilaria Martinelli
- Ing. Silvia Kull
- Dott. Massimo Bernabei
- Dott. Dante Chiappino
- Dott. Massimiliano Mariani
- Dott. Giovanna Trivella
- Dott. Silvia Burchielli
- Mrs Paola Celentano



16th June (Night) – S. Ranieri's Day (Patron of the City)

Furtheremore I wisk to thanks the European Commission for the financial support devoted to the SILCROTHANE project