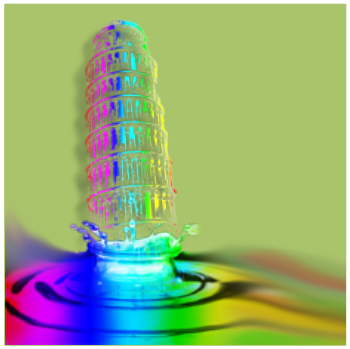
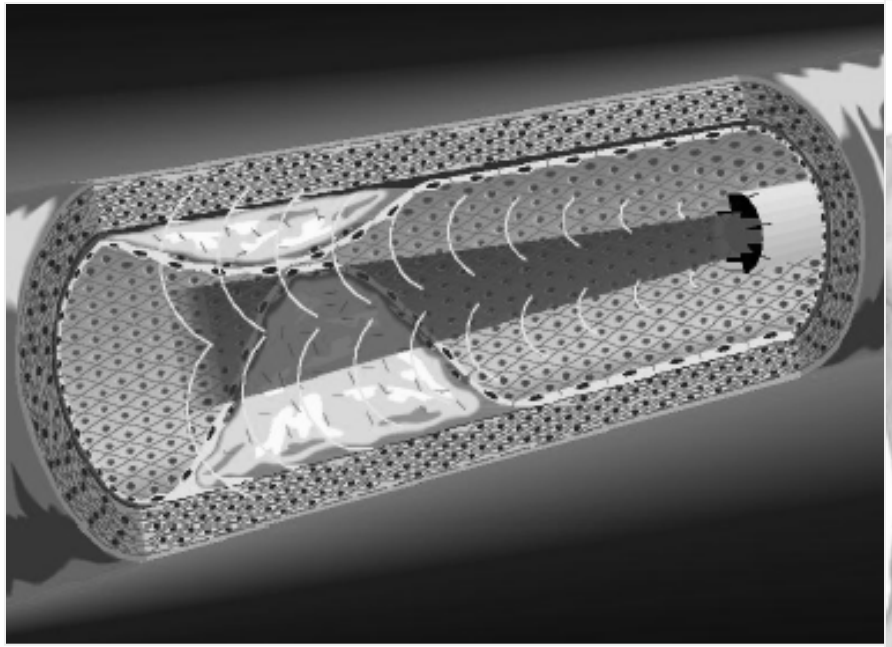



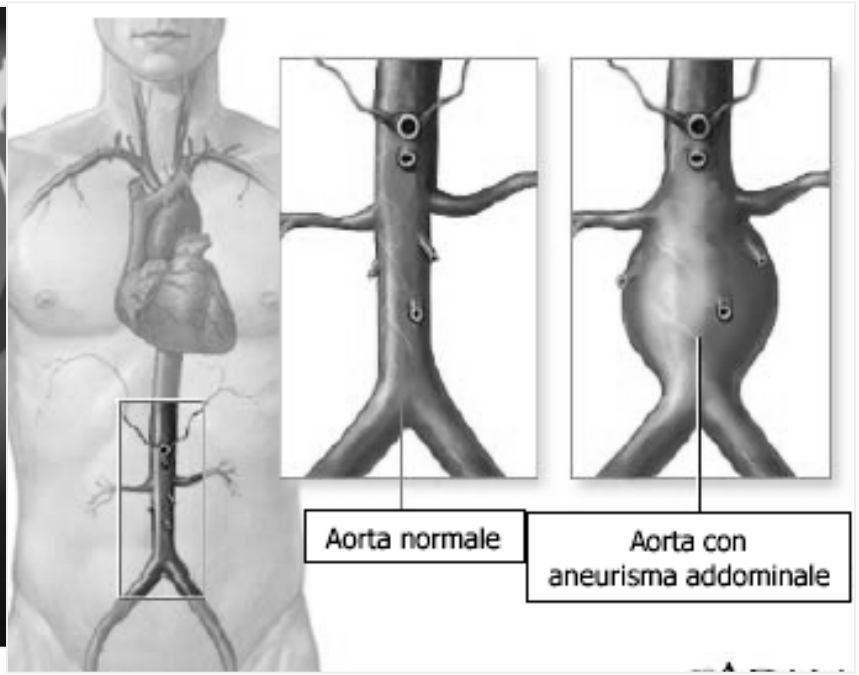
# Protesi vascolari

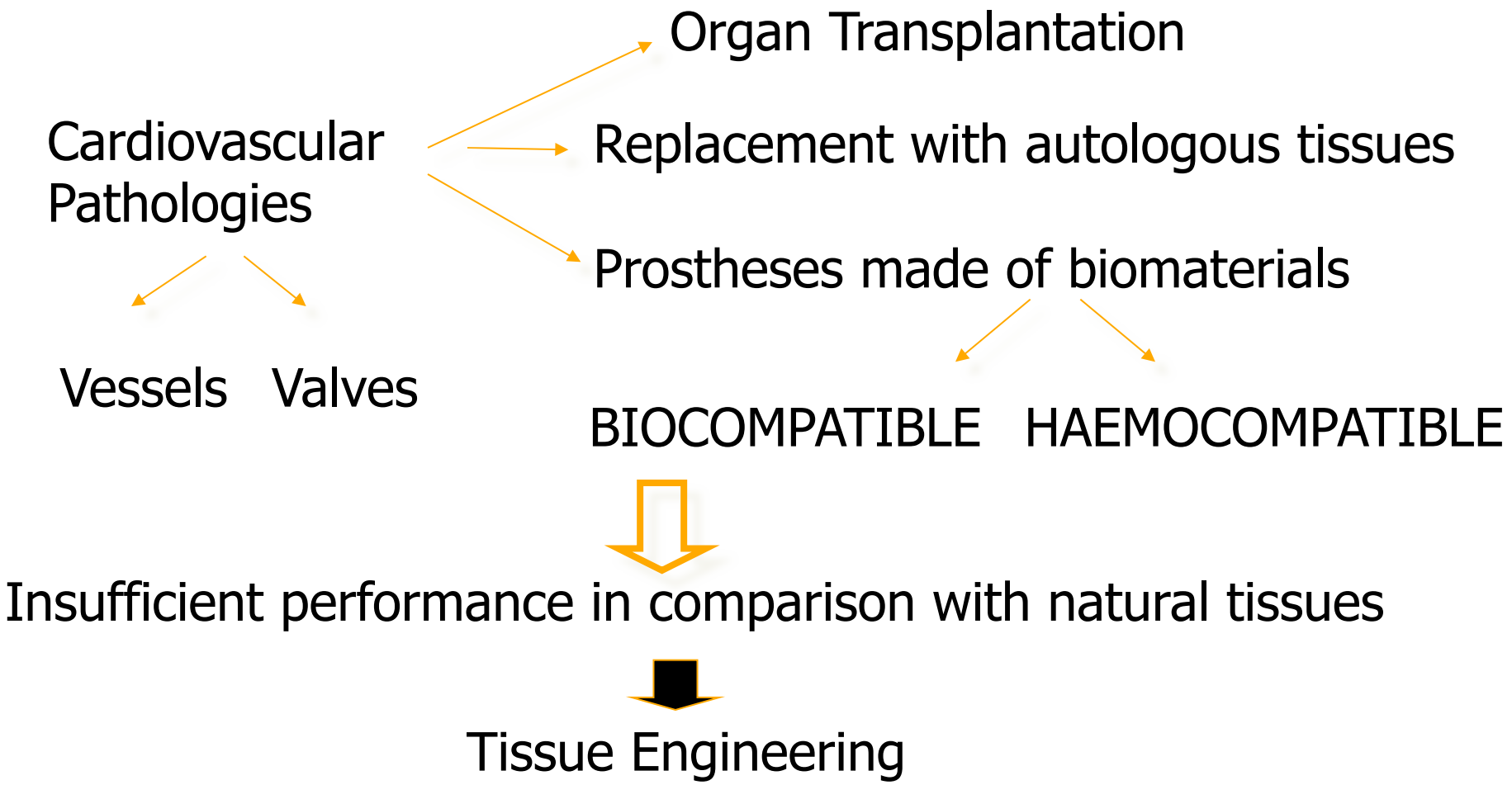
g.vozzi@centropiaggio.unipi.it

The VASCULAR PROSTHESES are medical devices that are permanently implanted in order to restore the efficiency of a vascular duct that, for any reason, is not more able to transport the blood correctly. The vascular implants are arterial systems: it depends on the fact that venous pathologies are much less frequent and serious because the venous pressure is inferior to that arterial (this fact reduces the vascular damage) and usually collateral circulations are generated that allow to venous blood to flow.

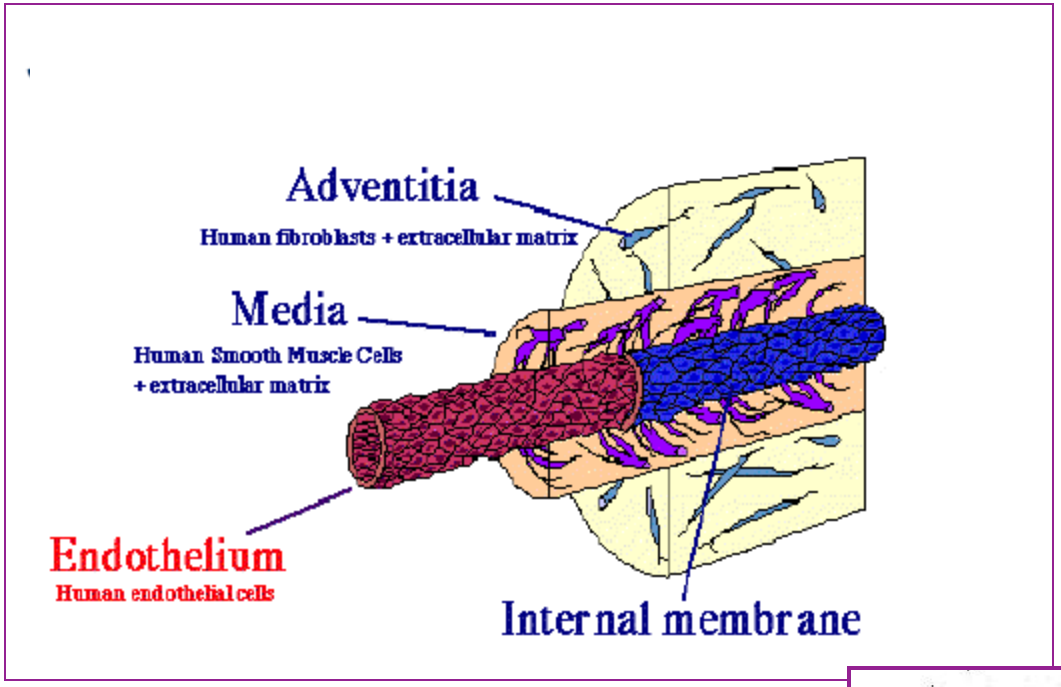
For the artery, the pathologies that require the use of vascular prostheses are: **STENOSIS and ANEURISM**.



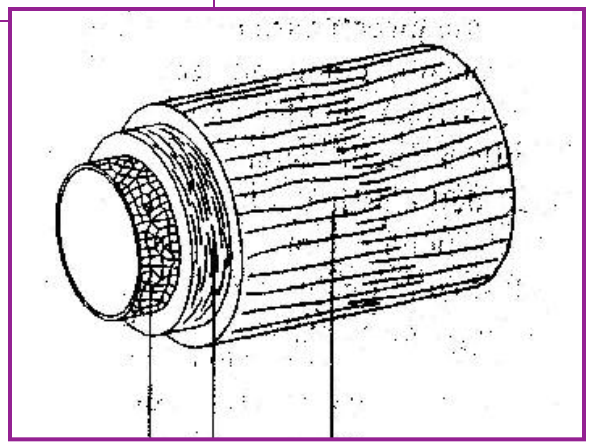



Organ Transplantation
Cardiovascular Pathologies
Replacement with autologous tissues
Prostheses made of biomaterials
Vessels
Valves
BIOCOMPATIBLE
HAEMOCOMPATIBLE
Insufficient performance in comparison with natural tissues
Tissue Engineering

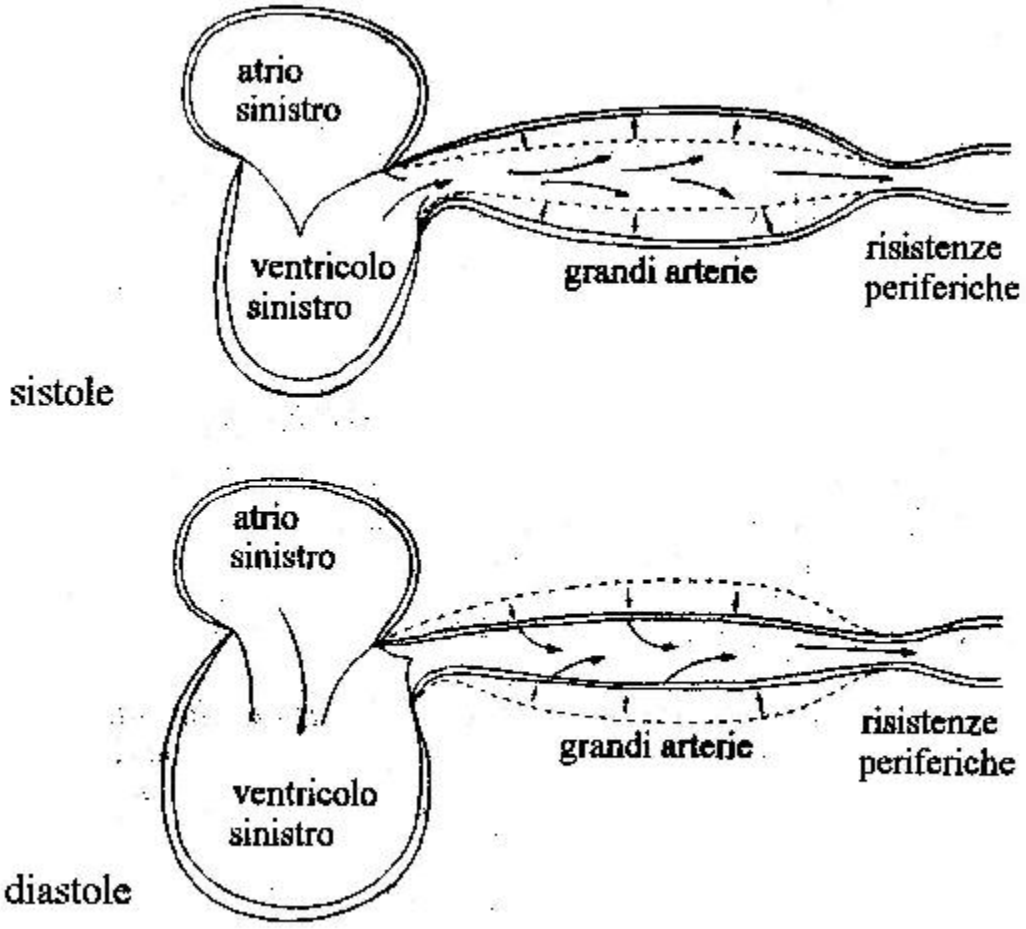
# Blood Vessels




- **Intima**: lining of endothelial cells
- **Media**: smooth muscle cells and circurlarly aligned fiber of elastin
- **Adventizia**: fibroblasts and connective tissue



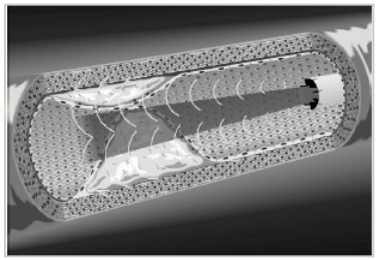
# Elastic behaviour of arteries:
## *shading of blood pulse propagation*

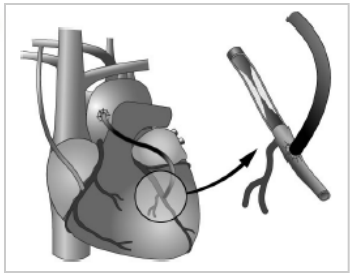


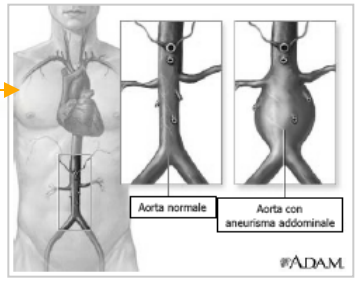
# Vascular Pathologies

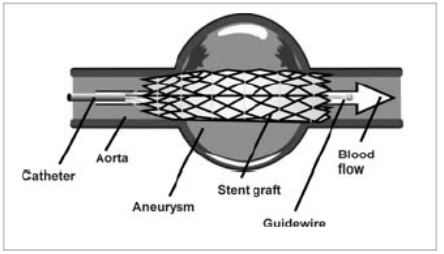
Implant of Vascular Prostheses

- Vascular Pathologies
  - STENOSIS
  - ANEURISM
- Trauma
- Dialysed Patients







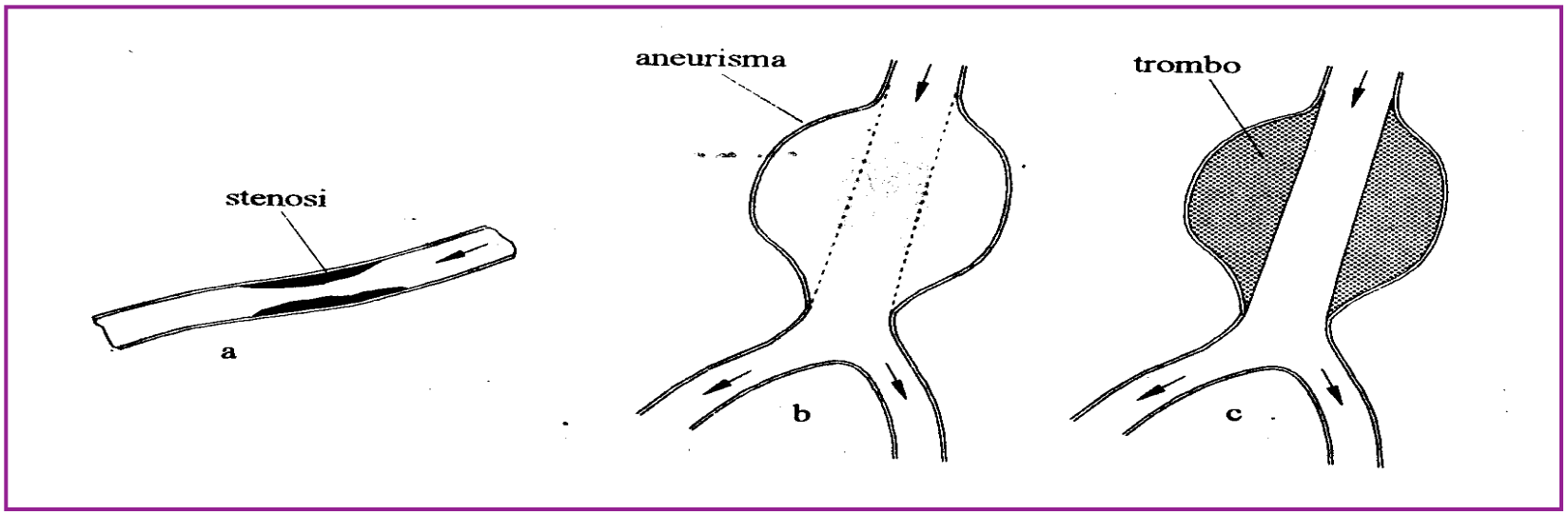



**Stenosis**: narrowing of the diameter of the artery caused by the increase of the atherosclerotic plate or by the generation of a clot; a stenotic artery is not more able to transport the blood towards the more peripherical districts and when the stenosis is serious the tissues after it become ischaemic.

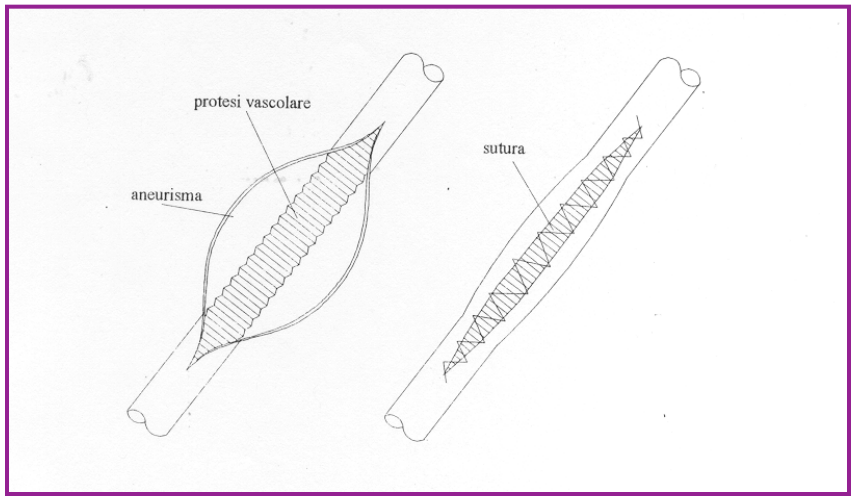
The ischaemia reduces or cancels the oxygen contribution to the tissue with possible necrosis;  in the organ hit by necrosis there is infarct, that it produces a partial or total loss of the function of the same organ.

**Aneurism**: increase of the artery caused by a progressive yielding of the vascular wall. The wall can be broken off provoking an inner hemorrhage and does not transport more the blood.

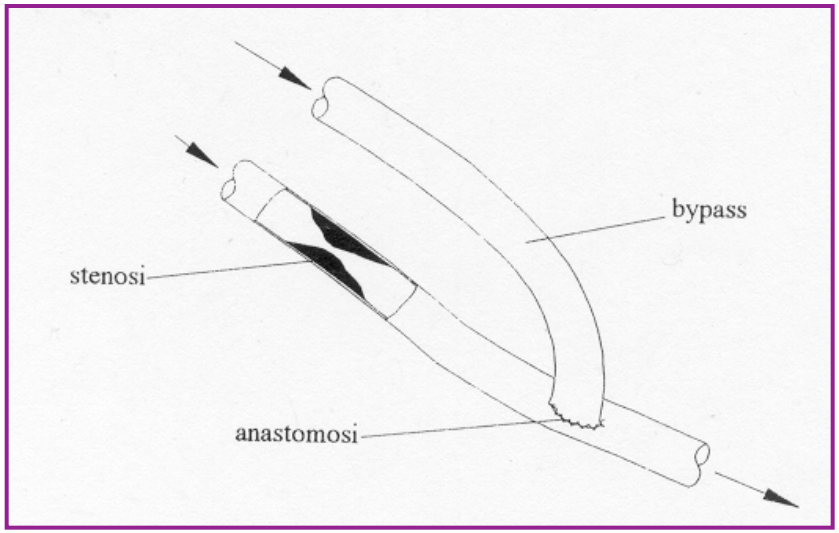
The aneurism causes moreover anomalous fluid-dynamic conditions, that can lead to the thrombosis of the expanded area.




## VASCULAR PROSTHESES FOR ANEURISM

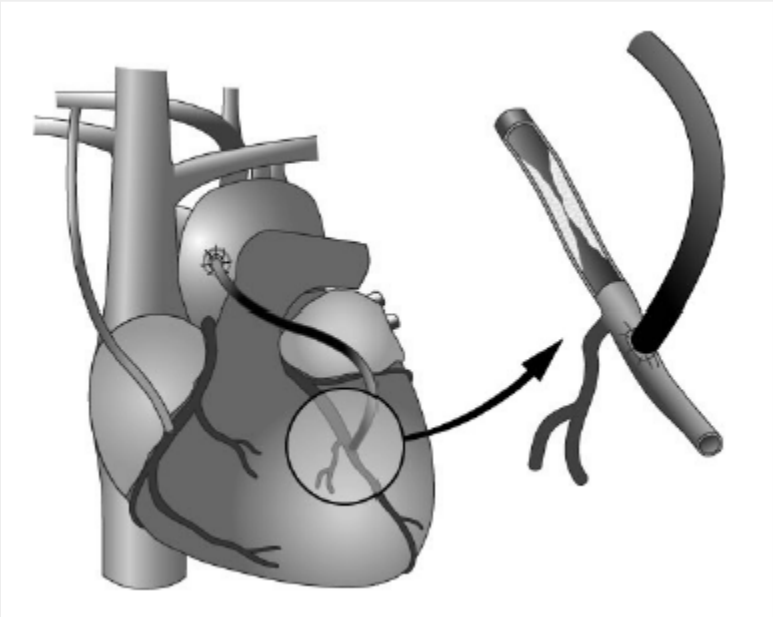



## VASCULAR PROSTHESES FOR STENOSIS



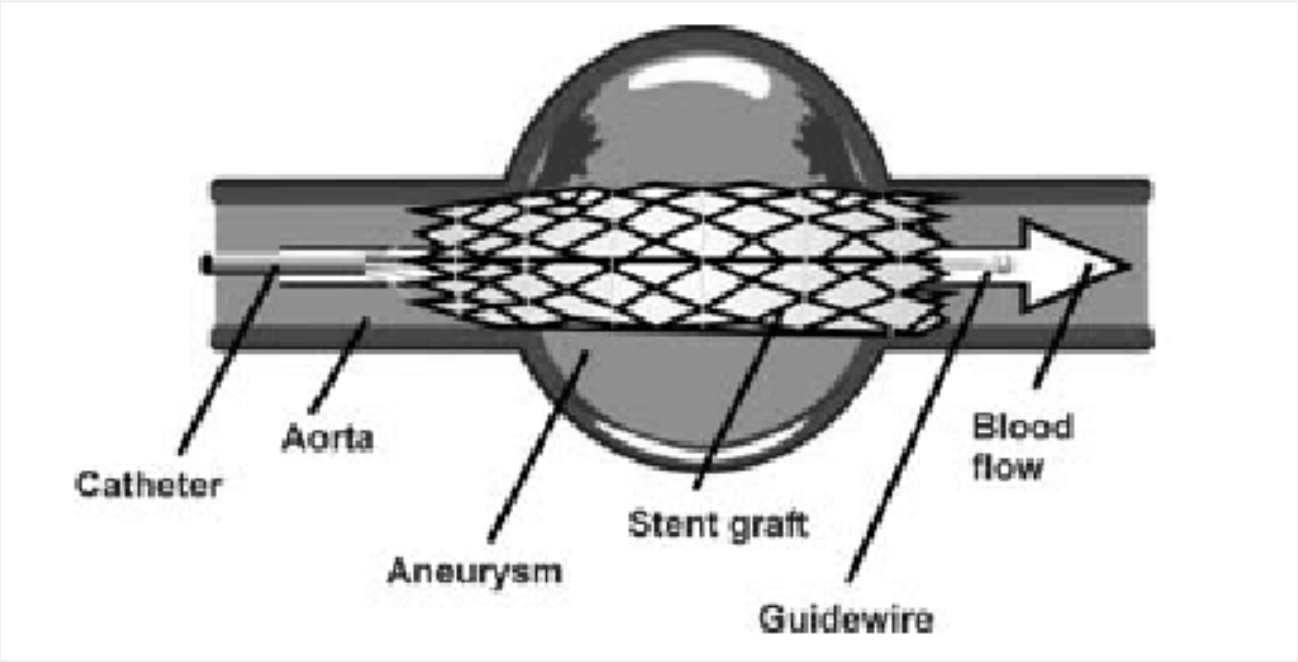
The implant of a vascular prosthesis allows to restore the correct conditions of flow and so to reduce the risk of break of an aneurism.

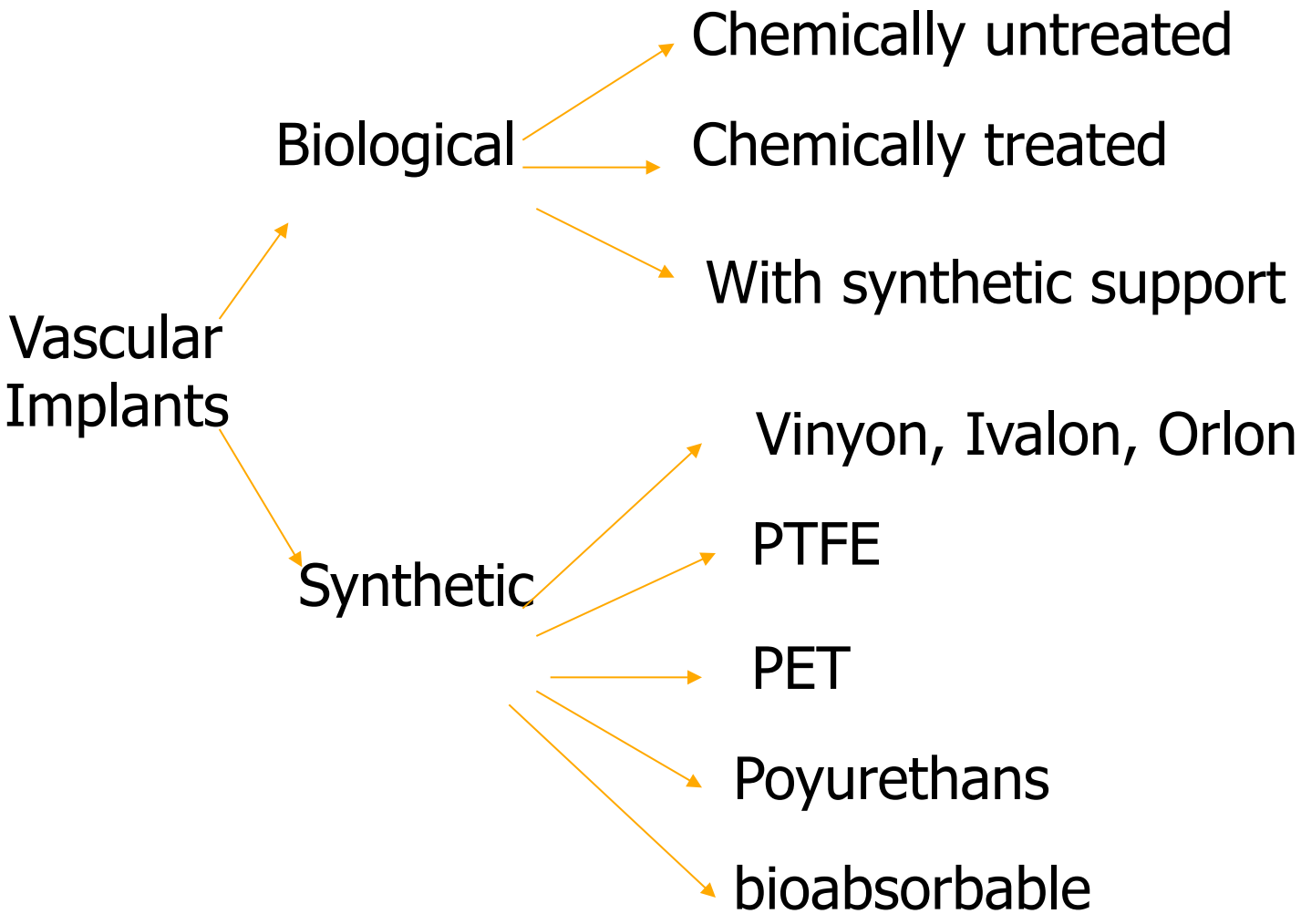
The prosthesis can be used to serve to pass the pathological zone (stenosis) and in this case it becomes a parallel branch.



In the case of an aneurism, the prosthesis is implanted in the blood vessel reducing its increasing.

Anastomosis is the suture between the prosthesis and the natural vessel.




Vascular Implants
Biological
Chemically untreated
Chemically treated
With synthetic support
Synthetic
Vinyon, Ivalon, Orlon
PTFE
PET
Poyurethans
bioabsorbable

***Important factors that determine the fate of vascular graft:***

- **Factors led to the patient:**

- Site of implant

- Size and course of pathology

- presence of other pathologies (diabetes, hypertension, tumors, infections....)

- Risk factors (smoke, problem with coagulation.....)

- **Factors led to the graft**

- Type and quality of material

- Technological design of the graft

- **Factors led to surgical implant**

- Technical factor led to the implant of the graft

# Ideal Characteristics of a graft

1. The duration of the graft must be greater than the life expectancy of patient.
2. The implant of the graft must not cause various undesired reactions different from those the patient is able to contrast.

## Essential characteristics for small diameter grafts:

- Smooth surface with a low friction coefficient and not thrombogenic.

- Porous wall promotes the regeneration of a neo-intimae layer
  - → haematic loss
  - → hyperplasia of intimae
- Techniques of precoagulation
  - → increase of thrombotic phenomenon
  - → infections
- Inner coating made of inert material (pyrolitic carbon),
  - → proofing
  - → poor regenerative processes
- Bioactive coating (Heparin, Growth factors)
  - → difficult to dose the activity and the quantity of drug
- Generation of a natural endothelium seeding endothelial cells inside the prosthesis
  - → inability of cells to remain adhered to the surface of prosthesis and proliferate

# How does it possible to obtain a non thrombogenic surface?

## 1. Non thrombogenic, smooth surface with a low friction coefficient.

The frictional, in fact, can produce local shear stresses that cause perturbations in the flow, and also turbulences, in proximity of the wall of the vessel. This can provoke the aggregation of plates and thrombosis. This process, than once primed is auto-spreading, is a serious problem more in prostheses with small diameter than in those to wide diameter.

Why??

- the fluid layer closer to the wall (the boundary layer) is proportionally more thick in small calibre vessels;
- the biological covering that shapes on the wall reduces the lumen and, in some small diameter vessel, acts as a stenosis.

# How does it possible to obtain a non thrombogenic surface?

## 2. Dimensions and mechanical properties of grafts similar to natural vessels.

In order to reduce disturbs in the flow the dimensions of prostheses and natural artery should be equal, and for an optimal transfer of pulsate energy also the elastic properties should be the same.

A bad anastomotic connection is inefficient and inefficiency in vivo is aggravated because each graft has two anastomoses.

The problem of prostheses is the compliance. The vascular prostheses are not compliant, and they do not simulate the mechanical behaviour of natural vessels.

NOTE: the compliance is a measure of the relaxation of an artery

$$\frac{\Delta V}{V} = \frac{\pi(R+\Delta R)^2 L - \pi R^2 L}{\pi R^2 L}$$

Expanding and simplifying, we get

$$\frac{\Delta V}{V} = \frac{2R\Delta R + \Delta R^2}{R^2}$$

Since $\Delta a$ is small, the higher power term can be neglected and hence, the volumetric strain will be given by the relationship

$$\frac{\Delta V}{V} = \frac{2\Delta R}{R}$$

Neglecting the factor 2, the compliance can be written as

$$C = \frac{\Delta a}{a \Delta p} \qquad (7.17)$$

# How does it possible to obtain a non thrombogenic surface?

**3. Generation of a natural endothelium seeding endothelial cells inside the prosthesis**

These attempts were failed because the cells are not able to remain adhered to the surface of the prosthesis and proliferate normally.

With the progresses of Tissue Engineering, however, many steps in ahead are being made in this direction.

# How does it possible to obtain a non thrombogenic surface?

## 4. Porous wall of prosthesis

It should promote the generation of a neo-intimae new completely natural surface = endothelium, BUT this does not happen in the correct way and around the anastomoses the neo-tissue grow in abnormal way (hyperplasia) and occlude the vessel

## 5. Use of internal non porous coatings

They are made of inert synthetic material, such as pyrolitic carbon, or opportunely functional. Attempts (binding chemically or physically an anticoagulant as heparin on the surface) gave insufficient results due heparin, the high cost, the lack of repeatability.

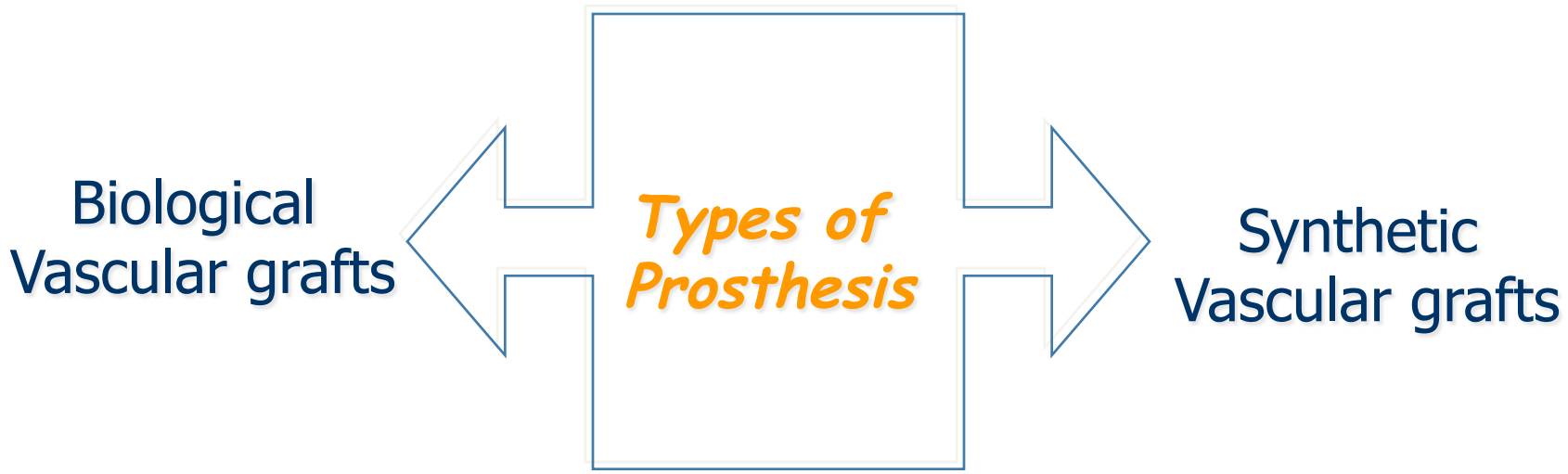
# *Advances……*

Although in ' 80 years large efforts have made in order to develop synthetic graft of small-calibre, only ' 90 in years they are been commercialised. Requirement of porosity, considered essential for an adapted tissue integration, involves the problem of the hematic losses, while the use of methods of precoagulation techniques of the prosthesis risks to aggravate the thrombotic phenomena and the infections.

# *Advances……*

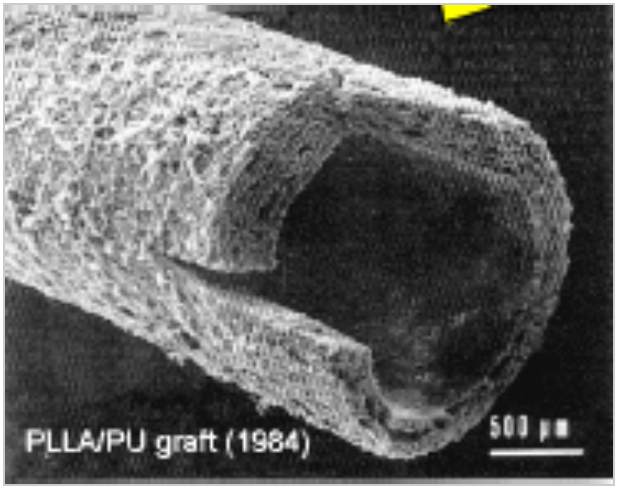
They have been gradually proposed "biocompatible" covers, waterproofing, with proteins (collagen, albumin, gelatine) or with synthetic hydrogels, but the results are not really good, as for technological as biological causes (poor processes of tissue regeneration).

Also the use of bioactive covers (heparin, growth factors) has been taken in consideration but still ideal clinical applications have not been caught up.


Biological
Vascular grafts
Types of
Prosthesis
Synthetic
Vascular grafts

# .....Bioresorbable Graft

The principle is to realize a graft that after the implant starts to degrade and simultaneously is replaced by natural tissue of the patient. The prosthesis developed at Groningen (Cell Tissue Res., 242, 569, 1985) was made of a blend of polyurethane-polylactic acid. It was microporous, compliant and bioresorbable.




However the application of a bioresorbable prosthesis implies that the cells are able to reconstruct a new artery and this seems at least problematic because the cells pertain to a sick artery. The research in this area is still a lot and the way towards the clinical application is still along

# Natural Vessels and Tissues

Numerous prostheses made with human tissues (auto and allograft) and animals (heterograft) have been tried:

a) frozen-dry arteries of human corpse;

b) chemically modified Bovine carotids;

c) human, fixed umbilical veins;

d) fibrous vessels manufactured on a rotary mandrel.

The success/failure of these prostheses has been varied. The walls, wit the exception of those of homologous vessels, are dead, and they come quickly replaced with poor fibrotic tissue. The bypass often show localized expansions (aneurisms) and, sometimes, breaches.

# Biological chemically untreated vessels and tissues

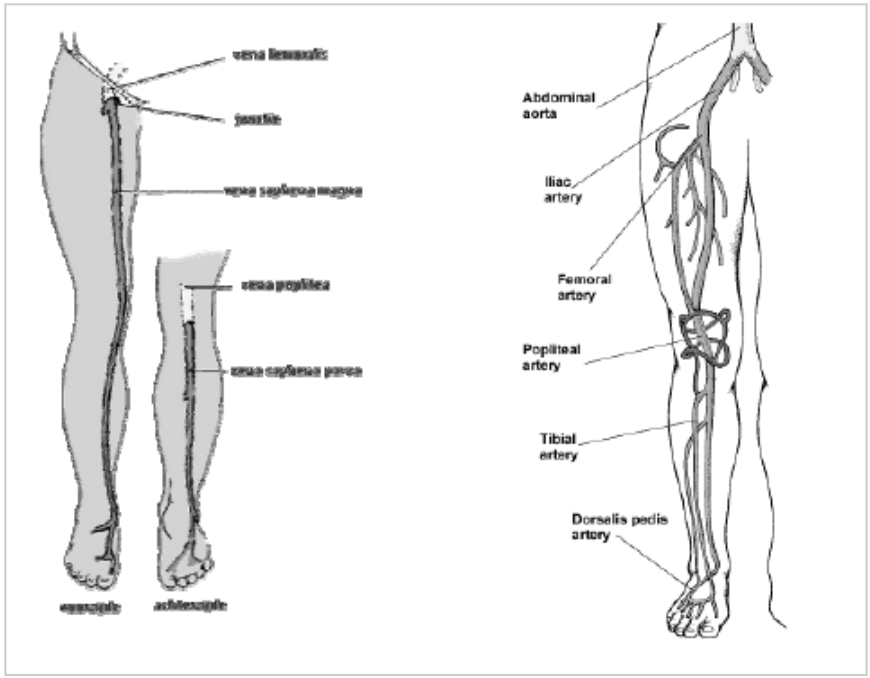
Today the autologous safena vein is optimal for arterial by-pass of diameter < 6mm, included distal arteries and the coronaries, while the autologous arteries (internal and external iliac artery, femoral artery, internal mammalian artery) are ideal for the bypass of the cardiac arteries and the peripheral arteries. Both systems introduce the disadvantage of the limited availability of donors.

# a) Autologous Safena vein

Advantages:

- Presence of a **lining of endothelial cells**
- Mechanical properties similar to those of natural arteries
- Absence of bacteria colonisation

Kunlin has realized the first bypass of safena vein in 1948, and the outcomes of this procedure have been satisfactory, infact from '50 years the use of venous grafts in the arterial system has been introduced in practical clinical. Later, Cartier and Hall have introduced in 1962 the technique of bypass in situ for the revascularisation of the inferior extremities. The principle of the bypass in situ is that to leave the safena in its place, reducing therefore the ischemic and surgical damage due to the removal of the vein and extending the short and long term permeability.



# Autologous Safena Vein

***Failure: 25-40%:***

- premature (within 30 days) for technical problems

- intermediate (30gg-24 months) as consequence of technical errors, fibrosis of the valves, hyperplasia

- late (> 24 months), secondary to progressing of atherosclerotic pathology.

The safena vein is not available as graft in the 20-30% of the patients who need bypass of the inferior extremities. Many bypass are distally anastomosed for the recovery of the limbs, only the autologous grafts are considered efficient in these areas and some surgeons do not use synthetic grafts for distal bypass but sometimes they prefer arrange more than an autologous vein in order to construct composed graft.

# b) Homologous Veins

The use of venous allografts is tried in order to repair peripheral arteries, in aorto-coronaric bypass and as secondary haematic access during the haemodialysis.

The results are controversial: the method of conservation of the vein is charged to influence negatively its long term permeability and there is the problem of the rejection associated to the antigenic answer, also the criopreservation does not eliminate the immunological reaction mediated by cells. It believes that the graft of homologous vein maintain their permeability only if their diameter is at least around 5 millimeters, because under this value there is the stenosis due to progressive thickening of the intimae wall one and to the fibrotic reaction of adventitia wall.

The immunotherapy can be help, however its effects on biostability of grafts are not known. The greater problem of the use of these graft is the variability and the unprectability of their physical and mechanical properties.

# c) Autologous Arteries

They are ideal substitutes of arteries, with good characteristics of long term healing.

- **internal and external iliac artery**
- **femoral arteries**
- **internal mammalian artery**

***Advantages*** : - ideal substitutes of arteries
- good characteristics of long term healing
- flexibility, vitality, stability

***Disadvantages*** : - not idoneous dimensions
- limited availability of donors

# Homologous Arteries

They have been firstly used to the beginning of the vascular surgery. They are taken by corpses and criopreserved. But they have been abandoned for the degenerative phenomena to which they had. The interest towards their use in case of infection of prostheses in the peripheral circulation has renewed (Bahnini, J.Vasc.Surg., 14, 98, 1991).

The idea is to take several arterial homografts by a donor of organs and to conserve them for a period of days or weeks to 4°C; in this way the graft would be available in order to replace an infected arterial prosthesis.

# Biological chemically treated substitutes (BIOPROSTHESIS)

The treatment consists in the “cross-linking" with gluteraldehyde (chemical cross-linking of collagen molecules). The treatment eliminates the antigenicits and increases the tensile strength, but also the embrittlement. The bioprostheses are not vital, and the endothelium lining is absent. The limiting factors are therefore the absence of reparative potentialities (healing) and structural embrittlement of the collagen wall.

# Biological chemically treated substitutes (BIOPROSTHESIS)

## a. Bovine Eterograft:

- Calf carotid

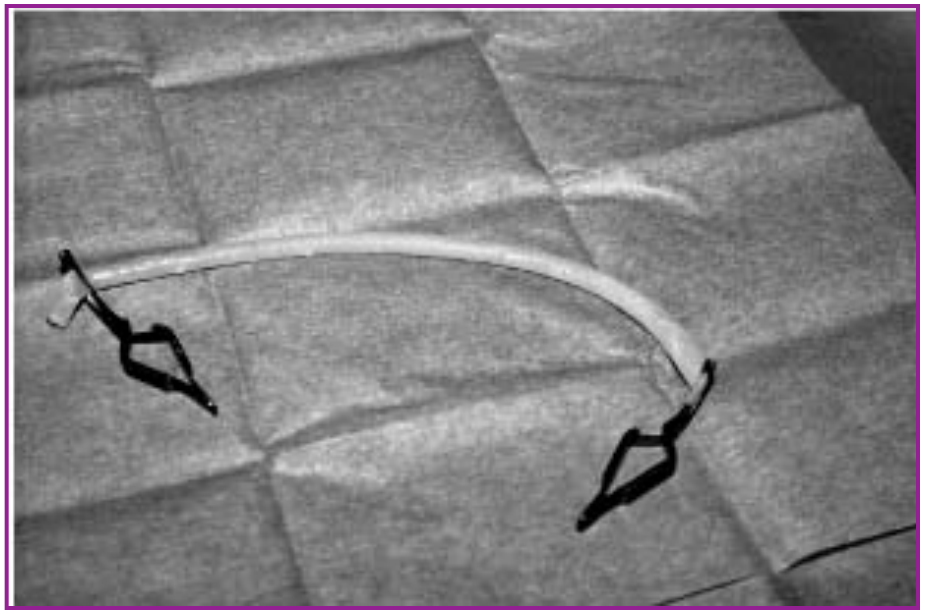
- Internal bovine mammary arteries

The principal complications are expansion, biodegradation (calcification, disintegration), infection and formation of cysts.

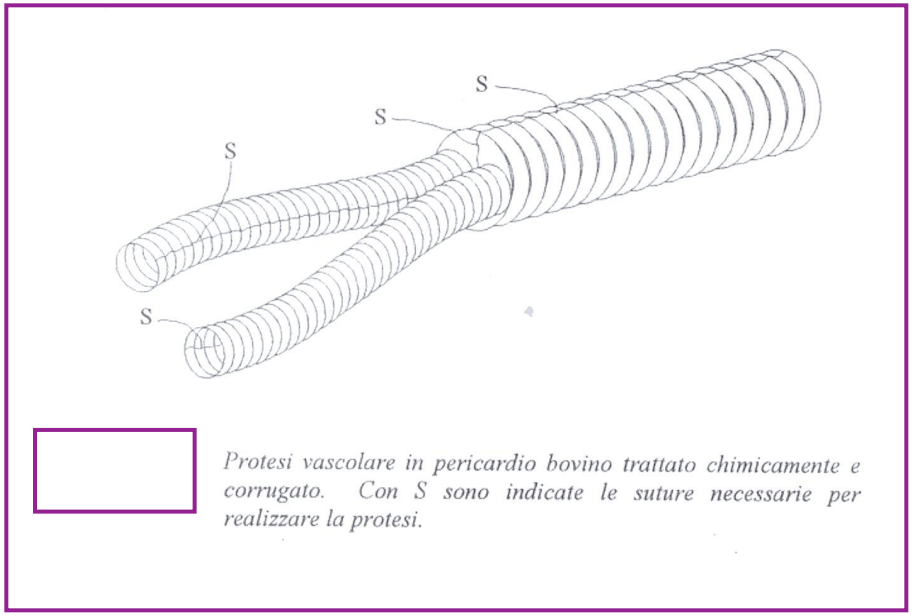
These graft are reserved to the patients that need procedures of secondary haematic access in haemodialysis, plasmaferesis and/or chemotherapy.

# Biological chemically treated substitutes (BIOPROSTHESIS)

## Umbilical Vein
## Bovine Carotid



## Bovine Pericardium




*Protesi vascolare in pericardio bovino trattato chimicamente e corrugato. Con S sono indicate le suture necessarie per realizzare la protesi.*

# BIOPROSTHESIS

## b. Human Umbilical Vein (HUV)

It is prepared cross-linking the collagen with gluteraldehyde. In order to increase the stability and to reduce the probability of expansions of collagen tube it is reinforced with a knitted polyester fabric (Dacron).

**Defects:** biodegradation of collagen, with progressive expansion and, in some cases, formation of aneurisms and bacterial colonization. There are problems associated to the lipid absorption that can favour the biodegradation process. The actual indications for the HUV are limited to their use as devices for haematic access and bypass of the inferior limbs when autologous vein is not available (alternatively to safena vein in patients with insufficient life expectancy).

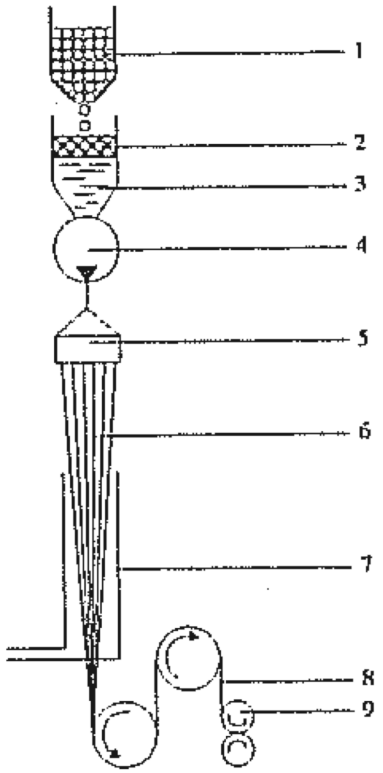
# MATERIALS

## Materials and synthetic fibers

The vascular prostheses manufactured with woven polyester (DACRON®, poliethylentereftalate) are used in the peripheral vascular surgery for the substitution of medium and large diameter vessels. The implants in aortic and iliac position have given a follow-up of beyond 15-20 years. The technological development is passed through various generations and various concepts and is in continuous evolution. However, the realisation of prostheses with a diameter inferior to 8 mm is not possible in Dacron for the facility of occlusion due to creation of thrombi.

The expanded PTFE (Goretex®, Impra®, ecc.) is famous and widely used as substitute of medium-calibre arteries (until 6-7 millimeters).

"Innovative" materials: polyurethanes, silicones and polyurethane-silicones.




*Processo di fabbricazione della fibra multifilamento in PET. 1: grani di PET; 2: riscaldatore; 3: PET fuso; 4: pompa; 5: filiera; 6: filamenti; 7: camera a vapore; 8: fibra multicomponente; 9: bobina di raccolta.*

# Synthetic Vascular Implants
## Mechanical Properties

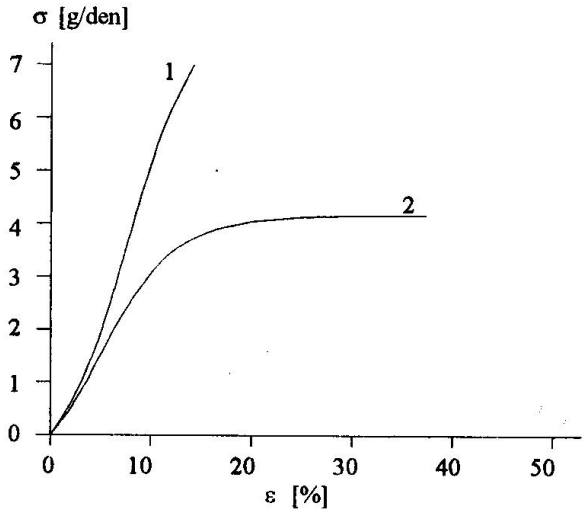



*Figura 8.8* *Caratteristiche sforzo-deformazione del Dacron stirato (1) e non stirato (2). Lo sforzo è in questo caso espresso in g/den dove den sta per denier che è la misura della sezione di fibra espressa come il peso in grammi corrispondente a 9000 m di lunghezza (da: L Harmon e MS Hoffman 'Fabrication and Testing of Polyester Arterial Grafts' in Vascular Gtaft Update, ed. KE Kambic, A Kantrowitz e P Sung, ASTM, Philadelphia, 1986).*

# Synthetic Vascular Implants

## EFFECT OF WRINKLING

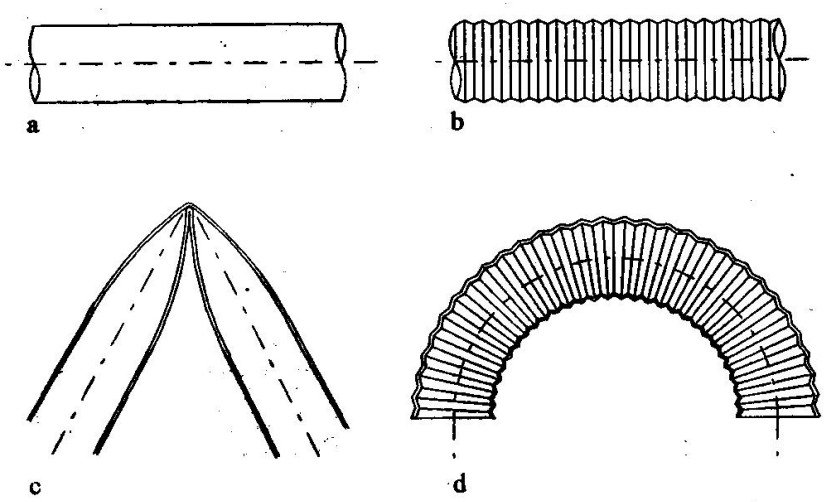
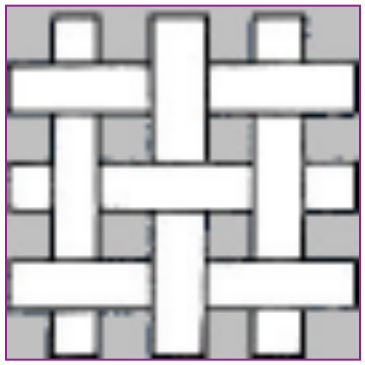
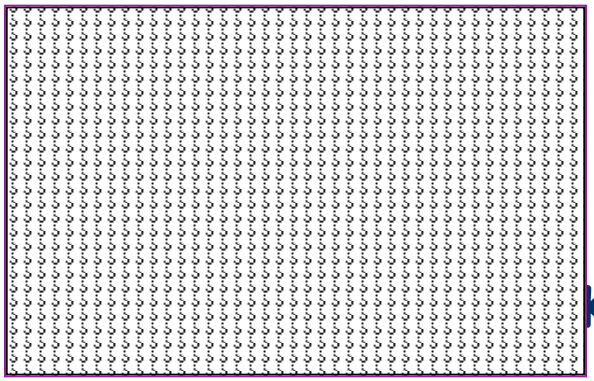



*Figura 8.12* *Effetto del corrugamento della protesi vascolare sulla sua flessibilità. La protesi non corrugata (a) tende ad occludersi quando viene curvata (c) mentre la protesi corrugata (b) consente curvature senza occlusione del lume (d).*

**Other important parameters: porosity, radial elasticity (compliance)**

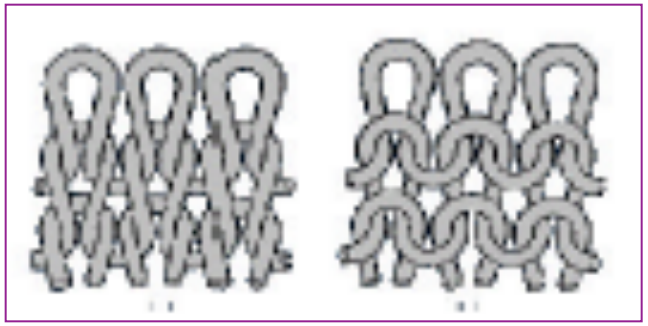
WOVEN





KNITTED

WEFT KNITTED



***Additional Technology**: the **velour** graft is composed of many filaments anchored to the surface of woven or knitted graft. I graft can be planar, with or without velour, or present internal, external or both velour.*

# Bioartificial Vascular Implants

Biological Polymers:
- High compatibility
- High costs of realisation
- Insufficient mechanical properties

Synthetic Polymers:
- High mechanical properties
- Low costs of realisation
- Poor biocompatibility

Bio-artificial Polymers:
- Good mechanical properties
- Good biocompatibility
- Low cost of realisation

PU + fibrinogen → Reticulation of fibrinogen With Thrombin and 13 factor → Material with good mechanical properties → Implant

Problem: generation of aneurisms

# PROBLEMS

BIOLOGICAL Prostheses
- Rapid aging (Hyperplasia, sclerosis, calcification)
- Degradation
- Infections

SYNTHETIC Prostheses
- Thrombogenicits of internal surface
- Hyperplasia close to the anastomoses
- Difference of compliance in comparison to the natural vessel
- Absence of lining of endothelial cells around lumen of vessels

Engineered vascular substitutes, ideal characteristics:
- Properties similar to vascular vessels
- Presence of anti-thrombogenic endothelial lining

# First Used Materials

**VINYON N** = copolymer PVC/acrylonitryle

**IVALON** = polyvinilphormale

**ORLON** = polyacrylonitryle

*First synthetic grafts do not incorporate themself in host tissues and produce thrombosis and generation of emboli.*

# Synthetic used materials

**DACRON R** (polyethylentereftalate)

*Results:*

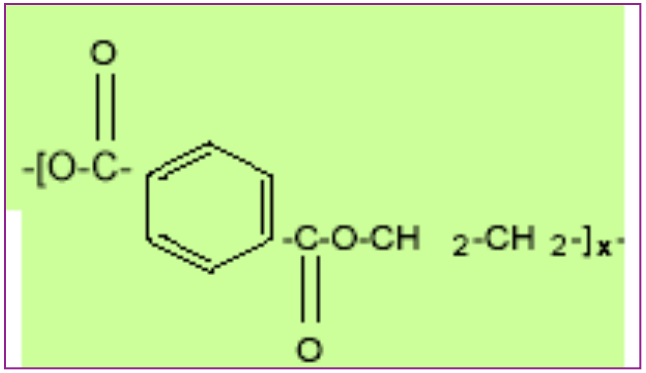
Long term success in 90% of implants in large vessels

**PTFE** (polytetraphluoroethylene)

*Results:*

Long term permeability in medium vessels, as second choose respect to biological substitutes

# DACRON




Type:

**WOVEN**

**KNITTED:**

***warp*** = fabricated in longitudinal direction, denser than weft, it resists to the unthreaded.

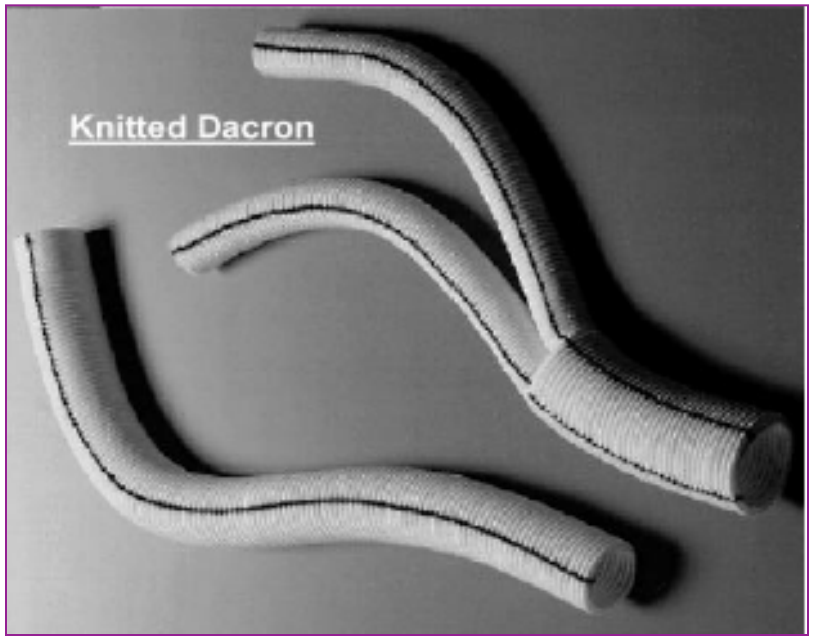
***weft*** = fabricated in radial direction, more flexible and stretchable than warp, it need precoagulation and it is more subject to expansion.

It must be avoided that woven of graft, once cut unthreads with worsening in the site of anastomosis.

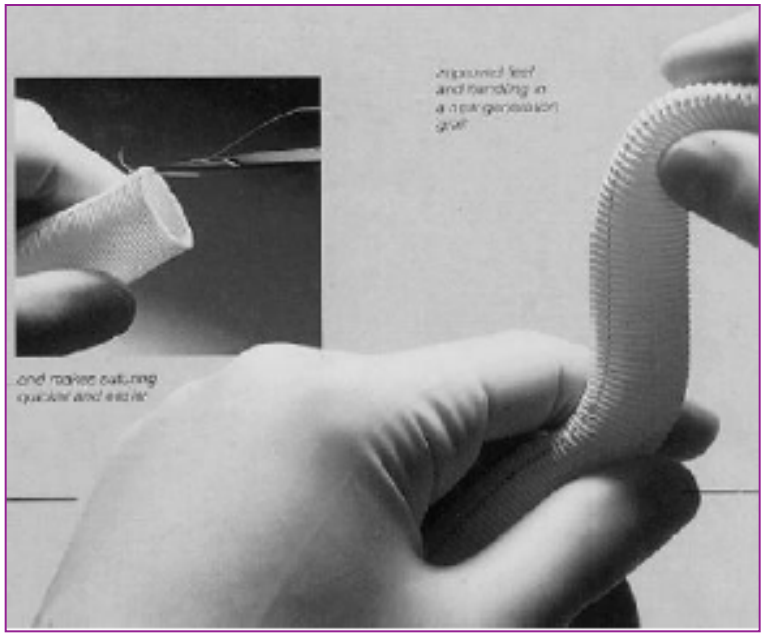
The woven prostheses are less porous. Low porosity produces an elevated rigidity, with consequent facility of calcification. There is a bad connection between the synthetic graft and the natural vessel.

The failure at anastomosis is easier.

# DACRON Prostheses




***Knitted Dacron***



***Woven Dacron***

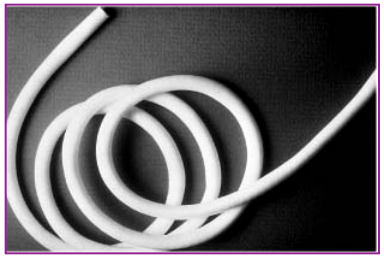
# PTFE Vascular Prosthesis

## A) *Woven* Teflon

$[CF_2\text{-}CF_2]_x$

The PTFE or Teflon prostheses have been designed with woven structure, that but it has been but discarded because charged of haemorrhages and formation of false aneurisms to the anastomosis. Some Authors (Couture, Guidoin ET To, Can.J.Surg., 27, 575, 1984) think that the use of suture in silk has contributed to these effects. The Woven Teflon has given less satisfactory results than the knitted TEFLON. The in-vivo and clinical tests has marked the absence of regeneration of the neo-intimae in woven graft, and not in that knitted graft. As the long term stability of the Teflon is better than whichever synthetic or biological material or biological.

Some researchers think that the realization of PTFE warp-knitted prothesis should take in serious consideration that are able do not unthreat at cut point.

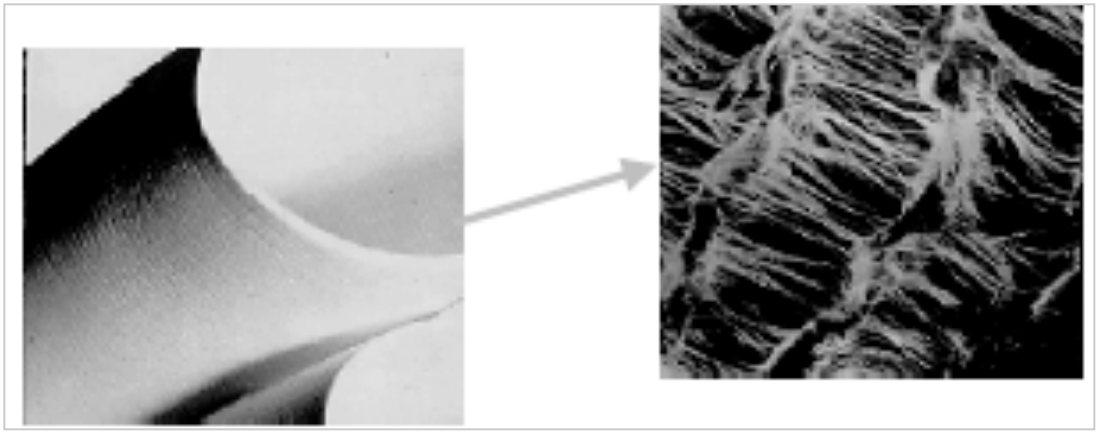


# Foam PTFE (Impra, Goretex, Vitagraft)

The Foam PTFE is widely used as substitute of arteries.

It is realised with a stirring process at high temperature that produces PTFE nodules interconnected with highly aligned fibres. Goretex graft has an external additional cover circularly aligned in order to increase the mechanical resistance, but this characteristic decreases the permeability of wall of the graft.

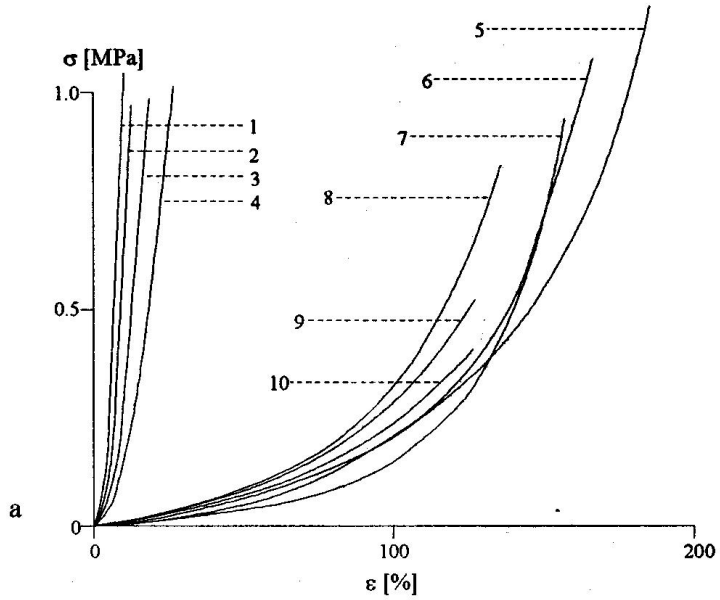
- **Poor compliance**
- **Thrombogenic without surface modification**
- **high stable**

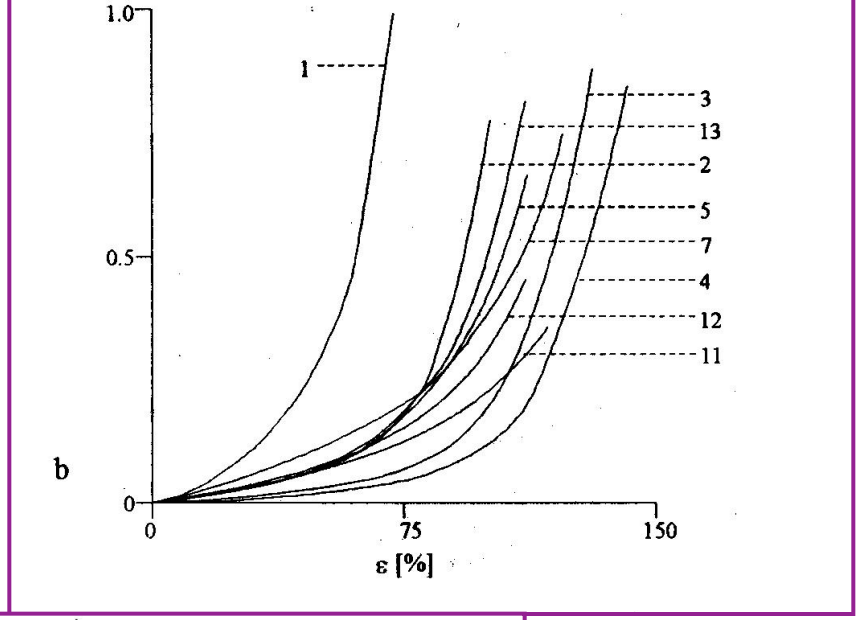


# Mechanical behaviour of PTFE Vascular Prosthesis

## COMPLIANCE

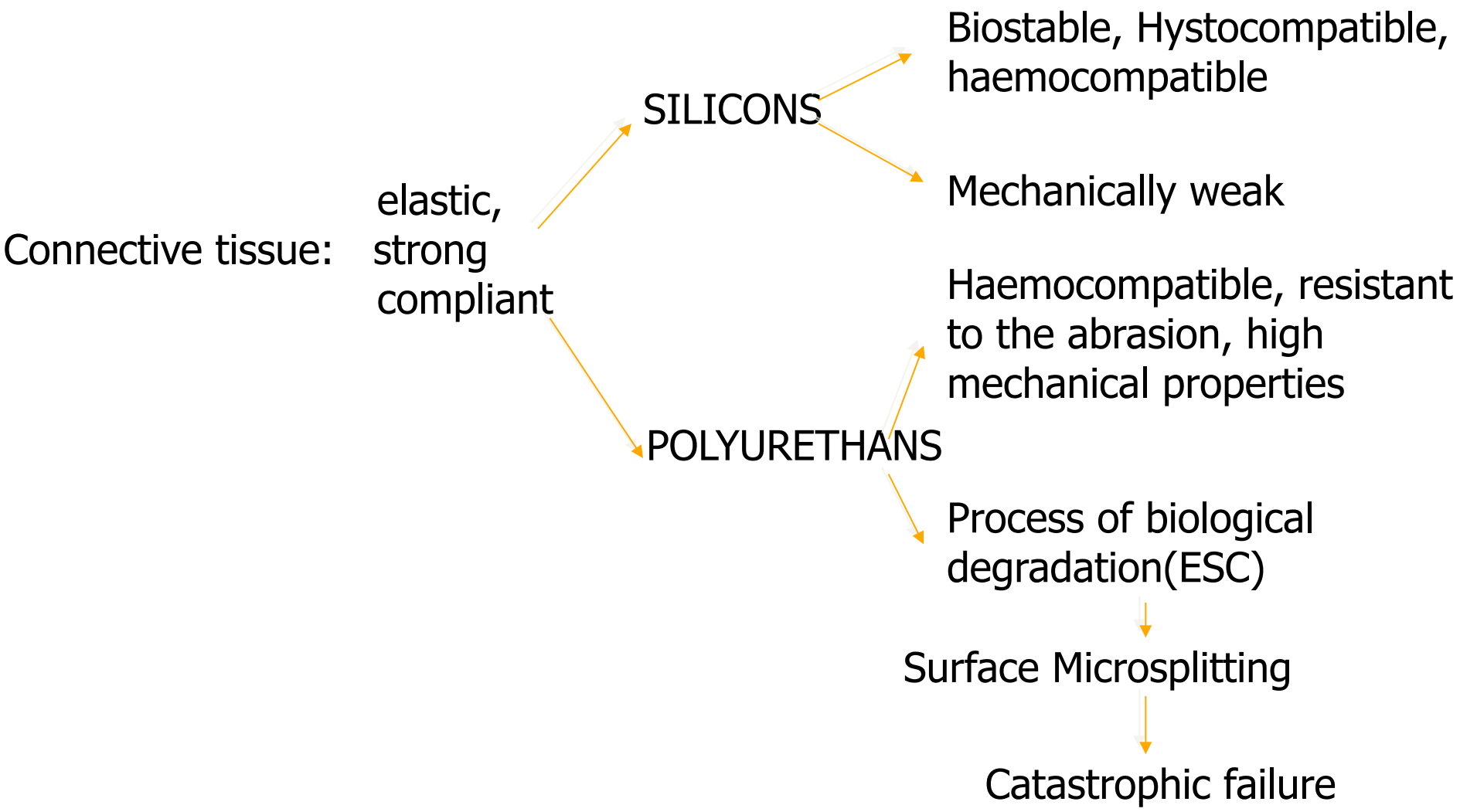
## LONGITUDINAL



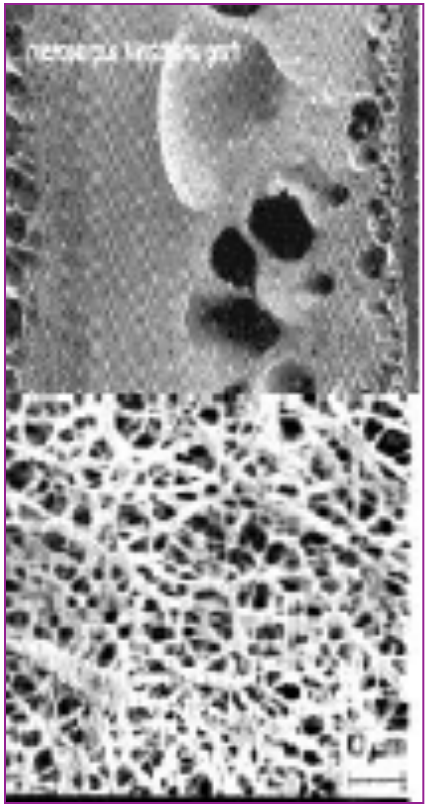

*Comportamento meccanico di protesi vascolari e, per confronto, di tratti di arterie. a: curve sforzo-deformazione in direzione circonferenziale; b: curve sforzo-deformazione in direzione longitudinale. 1: protesi in PET woven; 2: protesi in PTFE woven; 3: protesi in PET knitted; 4: protesi in PTFE knitted; 5: arteria iliaca; 6: aorta addominale distale; 7: arteria femorale; 8: aorta addominale prossimale; 9: aorta toracica distale; 10: aorta toracica prossimale; 11: aorta ascendente; 12: aorta toracica; 13: aorta addominale (da: M Hasegawa e T Azuma 'Mechanical Properties of Synthetic Arterial Grafts', J. Biomechanics, 12, pp. 509-517, 1979).*

# Alternative Materials: POLYURETHANS AND SILICONS



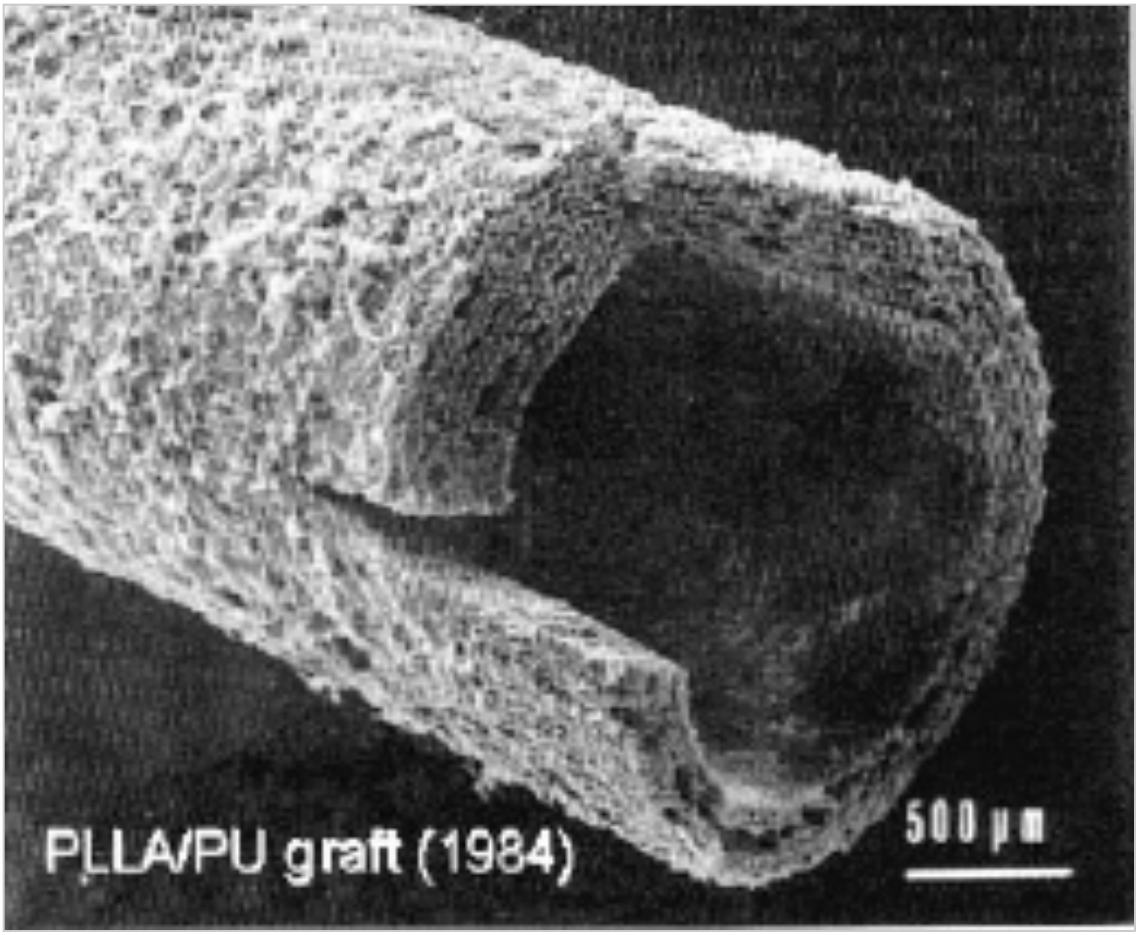
# POLYURETHANs

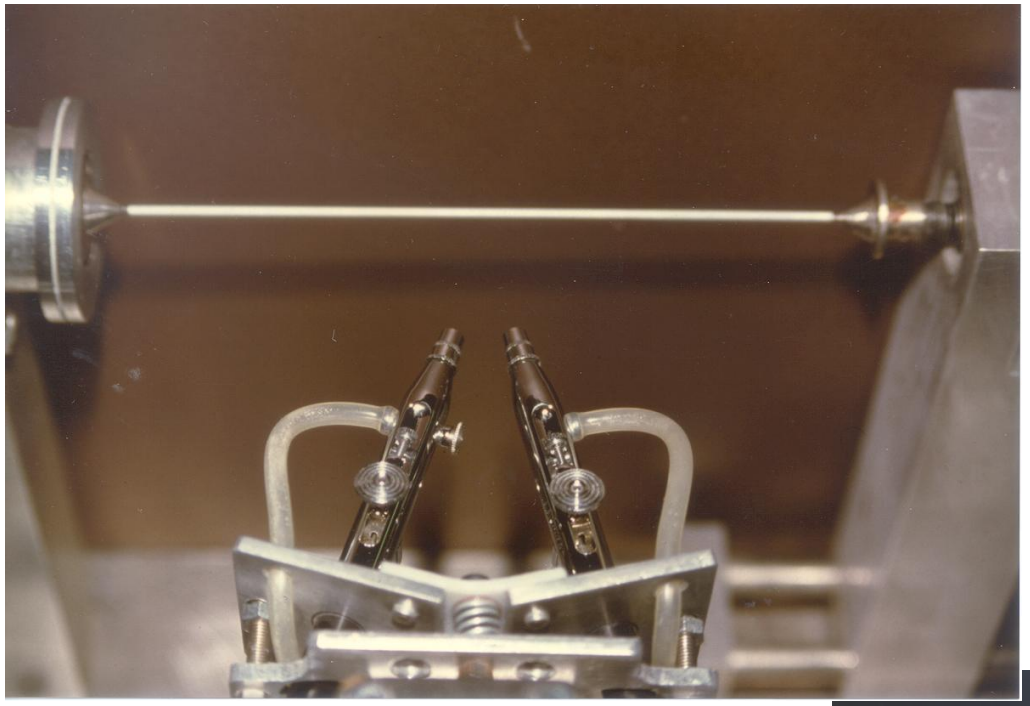
The category of polymer materials today collects more consents and attention is that of polyurethanes, thanks to the great structural versatility and to the easiness of manufacturing and to the optimal elastomeric properties that allow to construct tubular small-calibre grafts with modulated and opportune chemical-physical characteristics of radial compliance and haemocompatibility. Soft foam, fibres, tenacious and rigid covers can be produced. Grafts with better compliance can be constructed with several techniques (filament winding, solvent casting, depositions with technical spray, etc). On the basis of initial reagents polyurethanes more or less hydrophilic can be realised, or equipped of a surface that join hydrophobicity with hydrophilicity in order to encourage the specific protein absorption, or graftable with active molecules as heparin, polypeptides, etc, and with opportune physical property, compliance and stability.



**Wall with variable porosity obtained by filament winding**

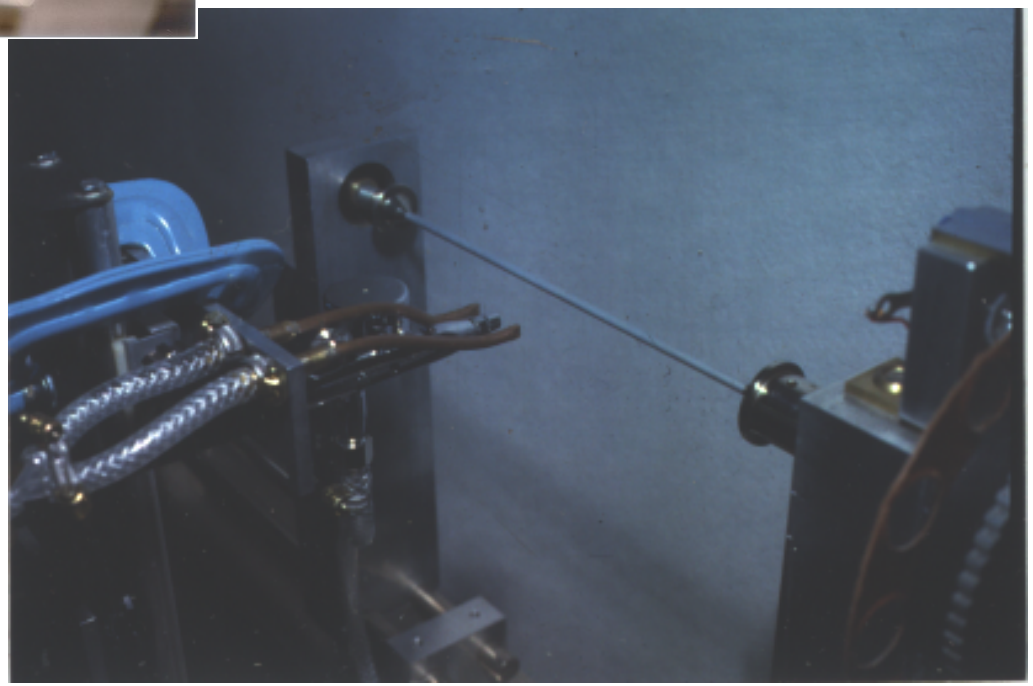
# Small diameter prosthesis made of POLYLACTIC ACID/ POLYURETHAN

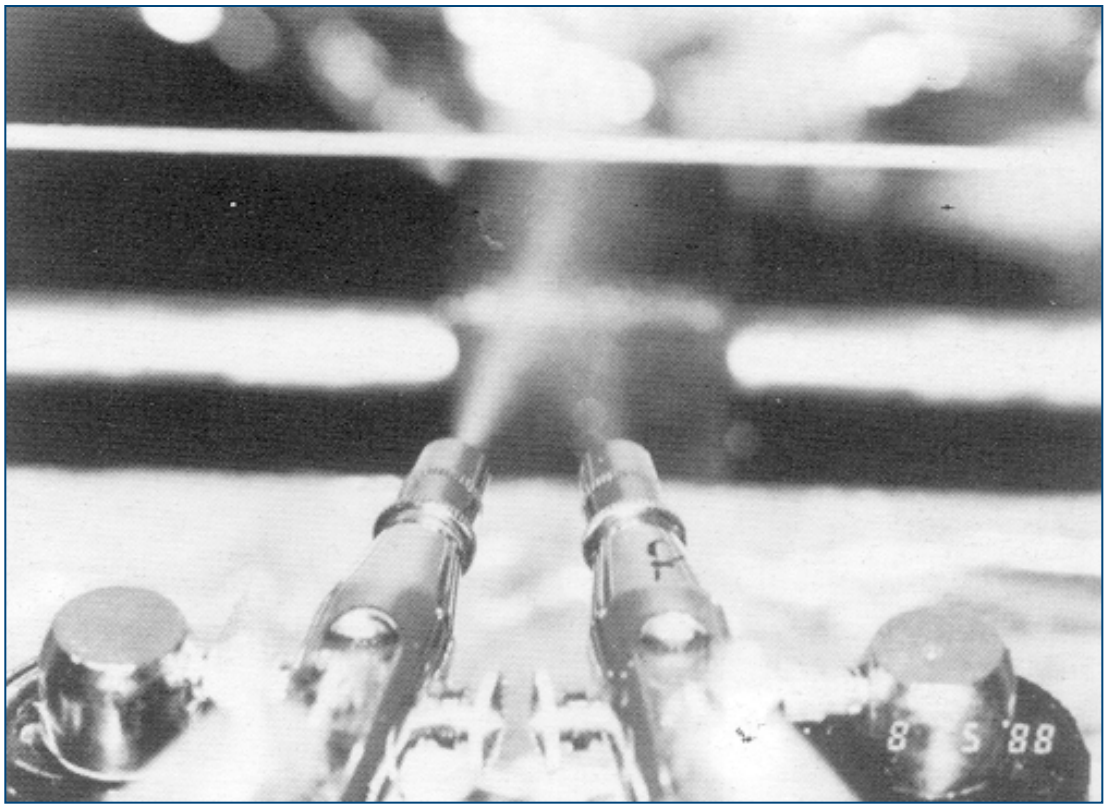




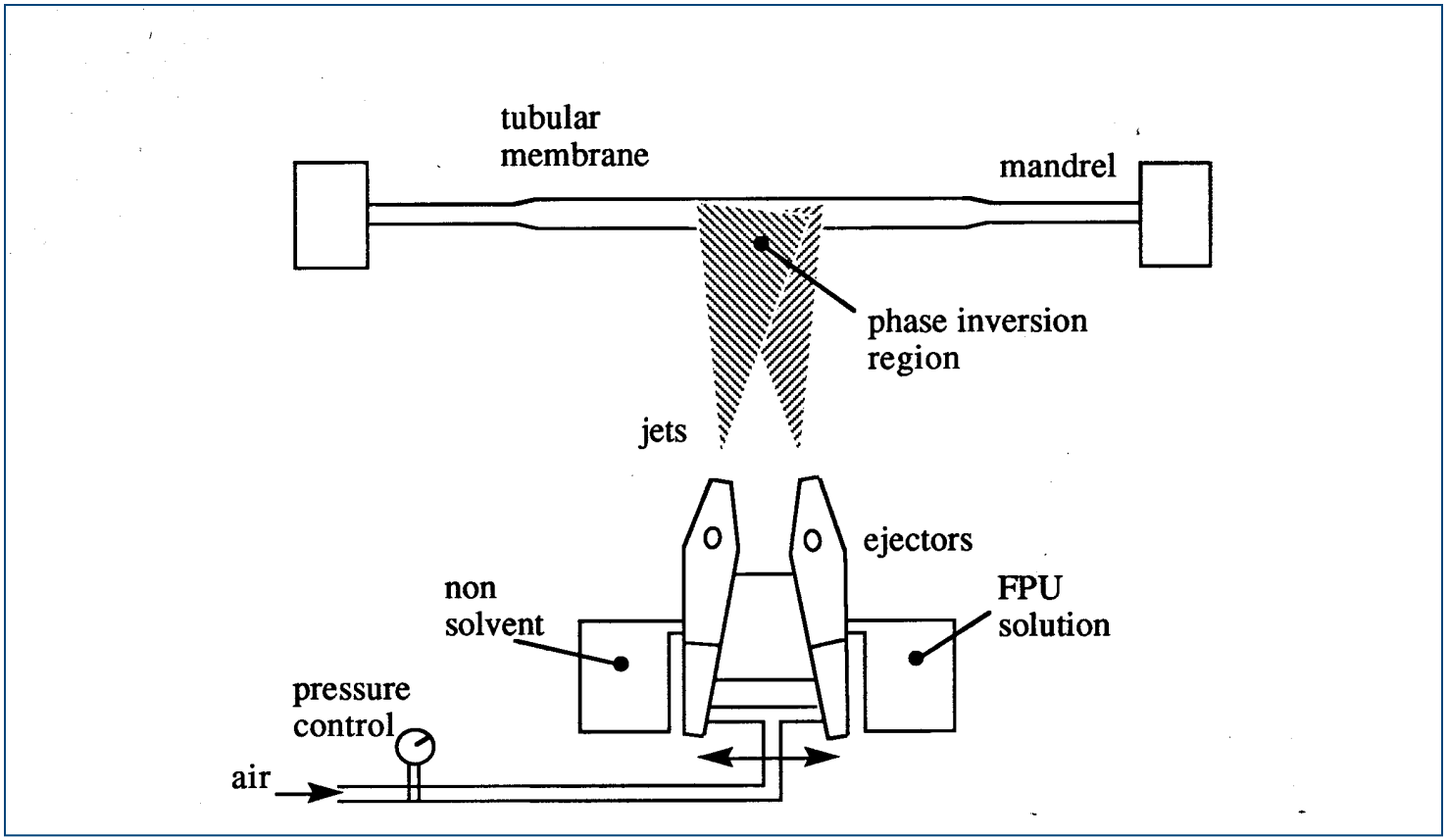
To fabricate the prostheses, we designed and built a small precision lathe in which mandrels of different diameters could be rotated at different speeds.

Parallel to the axis of the lathe we positioned a carriage which could move bidirectionally along the axis of the rotating mandrel, under the control of a motor which could be automatically reversed by the action of electromechanical elays controlled by micro-switches.

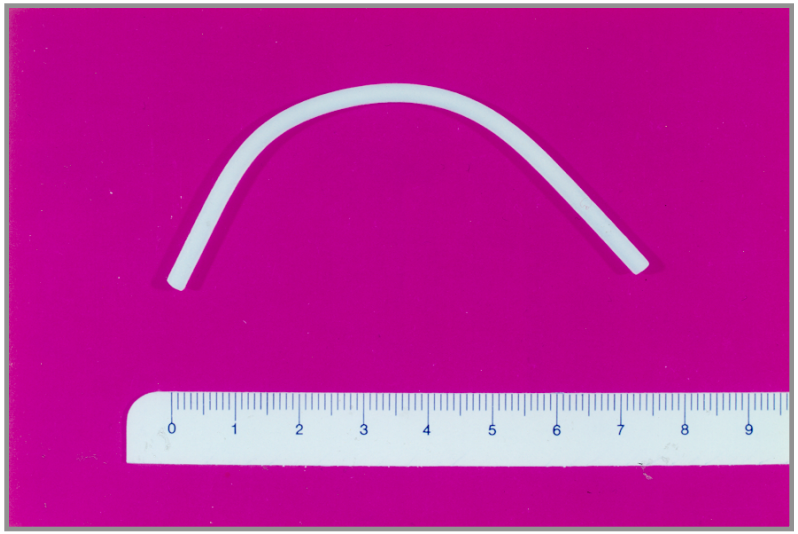


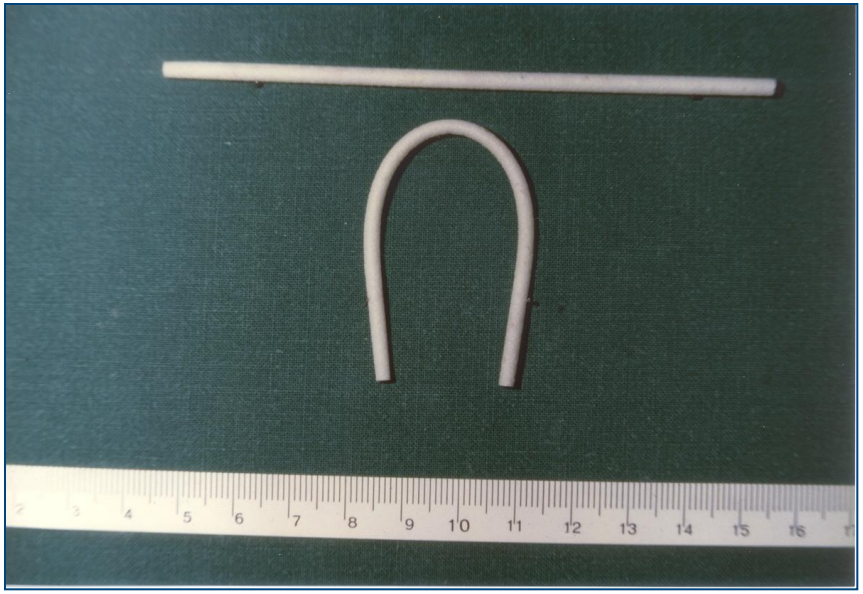


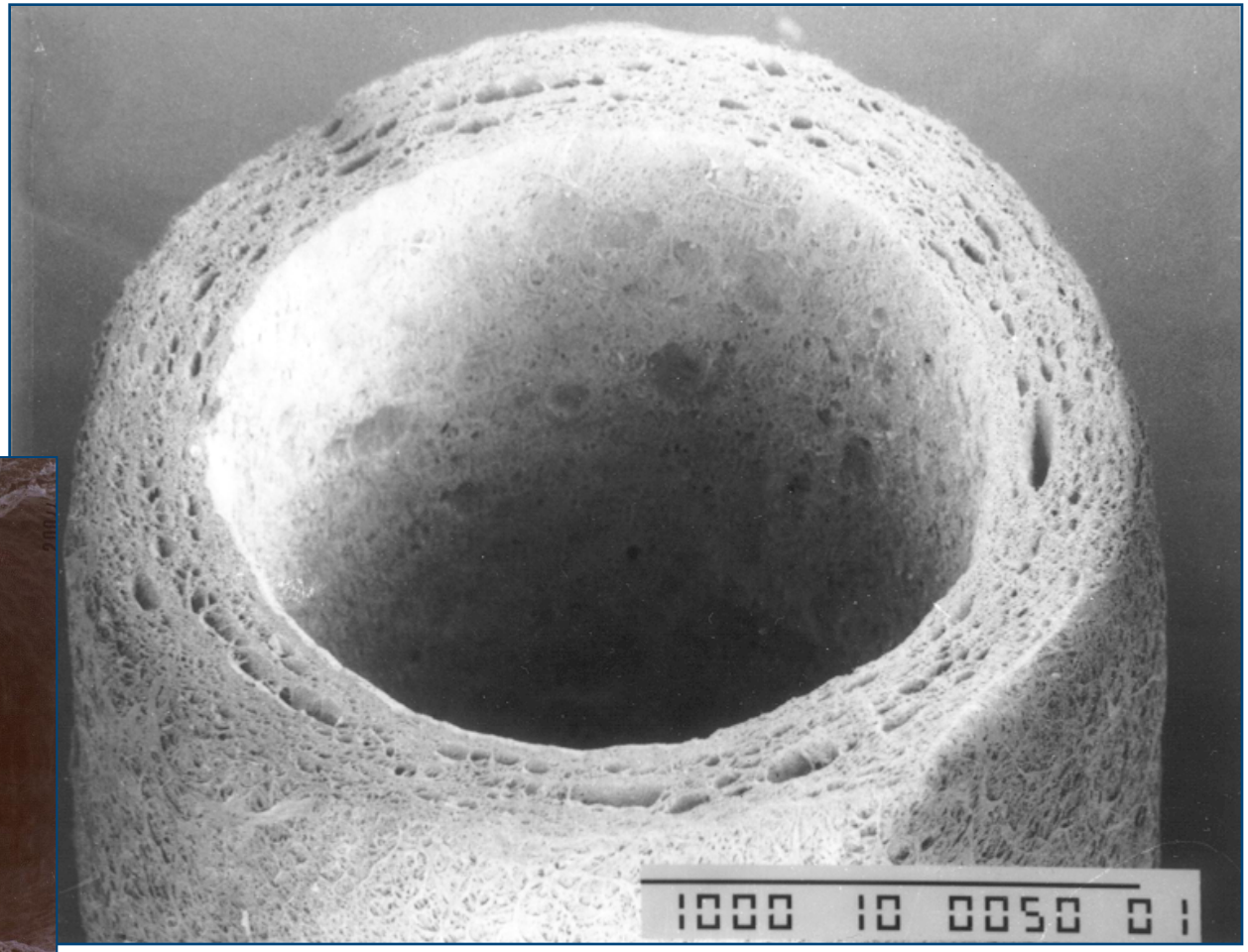
Two modified spray guns were mounted on the carriage and positioned vertically so that their nozzles were aligned with the longitudinal axis of the mandrel, at the distance and an angle from the mandrel such that the intersection of the jets occurred at the surface of the mandrel.

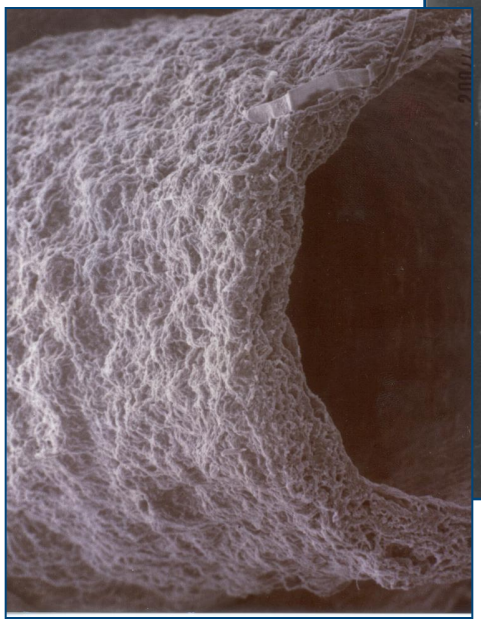



Scheme of the apparatus for the fabrication of tubular membranes


0 1 2 3 4 5 6 7 8 9


4 5 6 7 8 9 10 11 12 13 14 15



SEM of a bioprosthesis

(SEM of the small diameter vascular graft (internal diameter 1.5 mm)

# Vascular Graft

**TRADITIONAL**

- Haematic Transport
- Mechanical Resistance

**INNOVATIVE**:

Bioactive properties

Prevent the coagulation

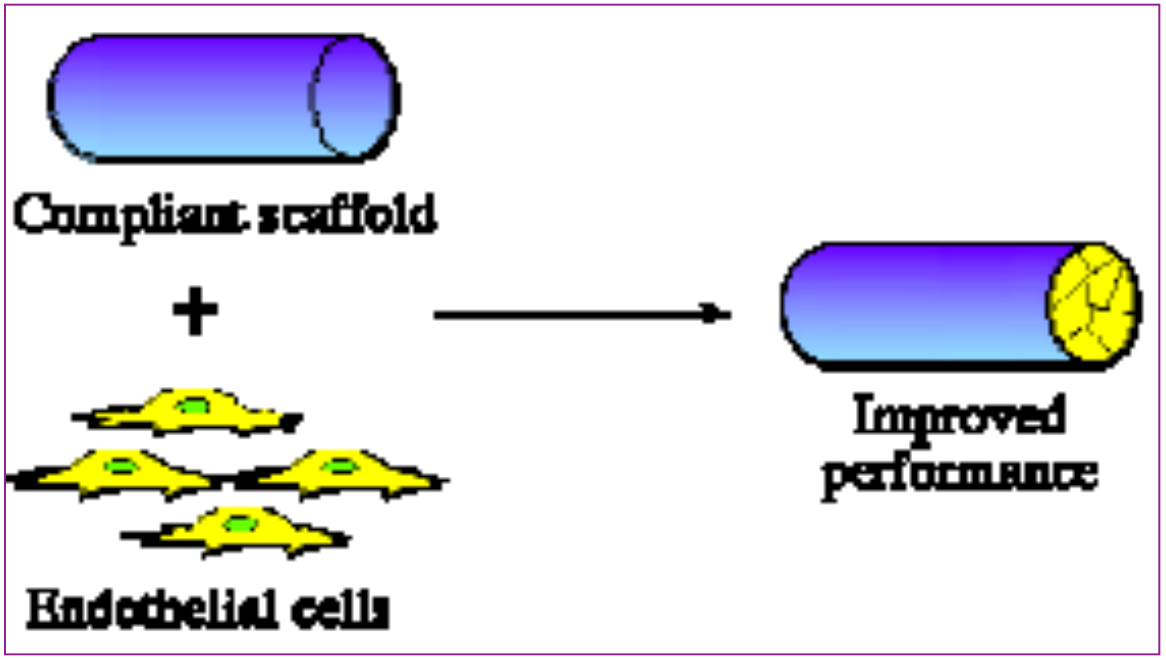
- support for endothelial cells
- Neovascularisation

# Blood Vessels: Tissue Engineering

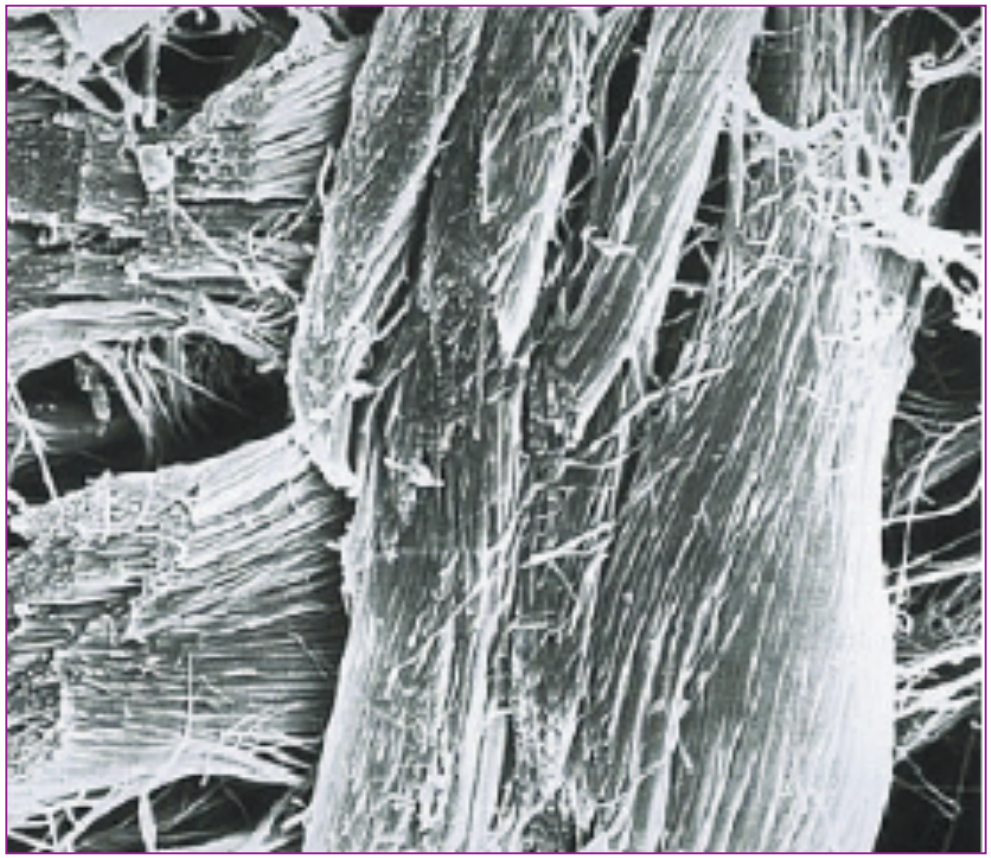
Many research groups are looking for the development of innovative grafts

(1)Designing synthetic non thrombogenic materials

(2)Engineering blood vessels using cells and scaffolds



# TISSUE ENGINEERED VESSELS



Collagen tubular scaffold seeded with smooth muscle cells and endothelial cells

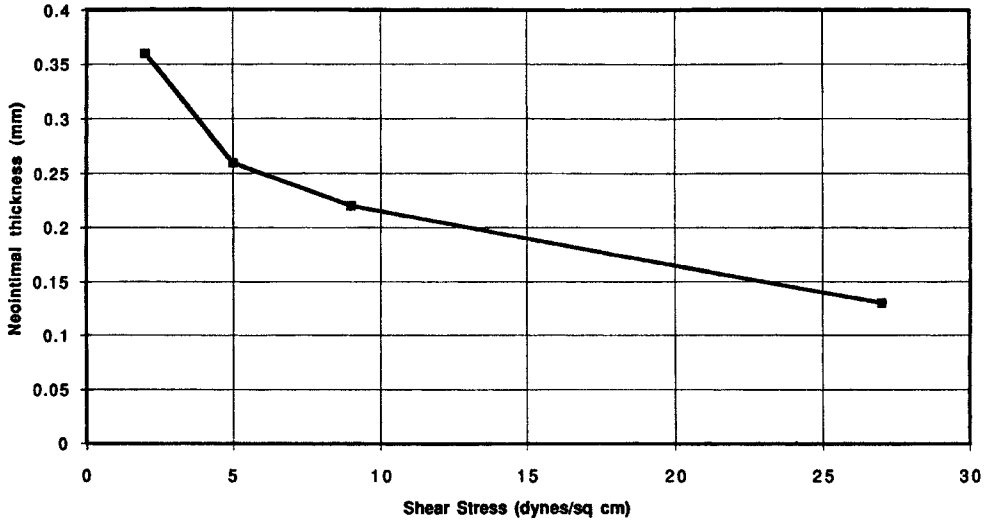
# CHARACTERISATION

The characterization of prosthesis is made evaluating the following parameters:

1. compliance,
2. permeability
3. porosity,
4. resistance to tensile stress,
5. resistance to burst
6. duration

La velocità di propagazione ($\nu$) delle onde si pressione dipende dalla elasticità della parte dei vasi (E), dal loro diametro (D) e dalla densità del sangue ($\rho$) [Legge di Moens-Kortewerg]

$$\nu = \frac{E\,s}{\rho\,D}.$$




$$\text{Intimal thickness} = A \times \frac{1}{\text{wall shear rate}} + C$$