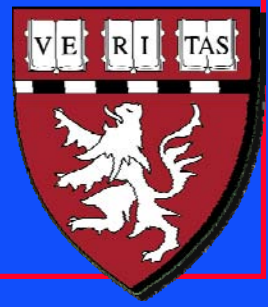
Massachusetts Institute of Technology
Harvard Medical School
Brigham and Women's/Massachusetts General Hosp.
VA Boston Healthcare System



2.79J/3.96J/20.441/HST522J

EPITHELIALIZATION: ENDOTHELIALIZATION

M. Spector, Ph.D.

BLOOD VESSELS

- **Permanent biomaterials for the fabrication of vascular prostheses**
- **Biomaterials for scaffolds for blood vessel tissue engineering**

Epidermal Wound Healing

Diagrams of healing process (cell migratio.., mitosis) removed due to copyright restrictions.

Vein

Artery

Intima

Endothelial cells

Diagrams of removed due to copyright restrictions.

Media

Smooth muscle cells

Adventitia

BLOOD VESSEL HISTOLOGY

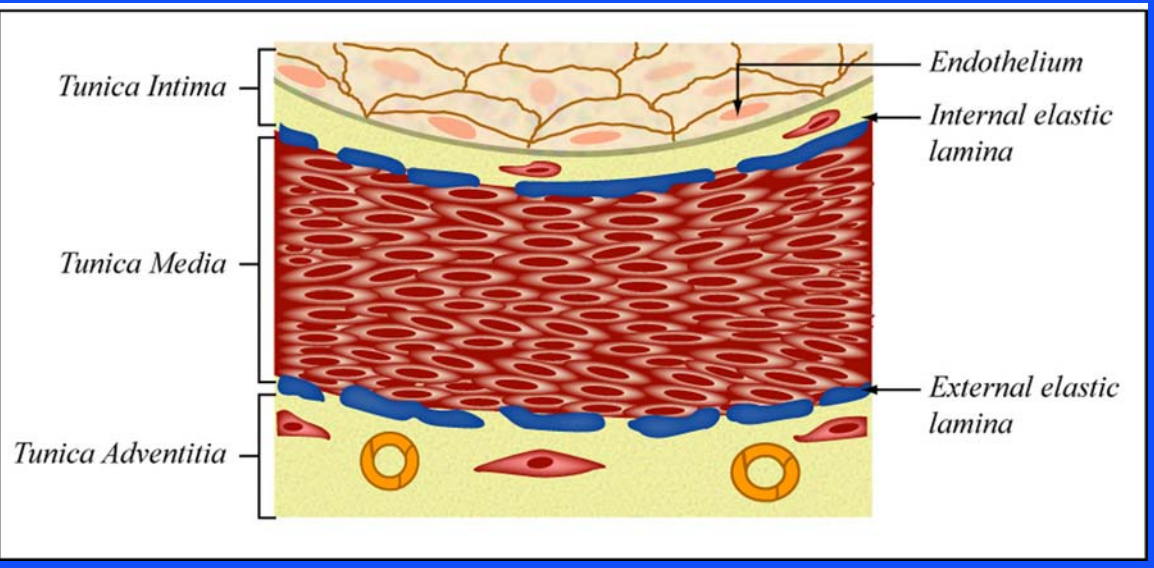


Figure by MIT OpenCourseWare.

- Tunica **intima**
  - single layer of endothelium
- Tunica **media**
  - circumferential layer of smooth muscle cells
- Tunica **adventitia** (externa)
  - fibrous connective tissue

EXAMPLE OF A HOLLOW, LAYERED STRUCTURE
THE VASCULAR WALL

Diagram removed due to copyright restrictions.
Detailed structure of vascular wall.

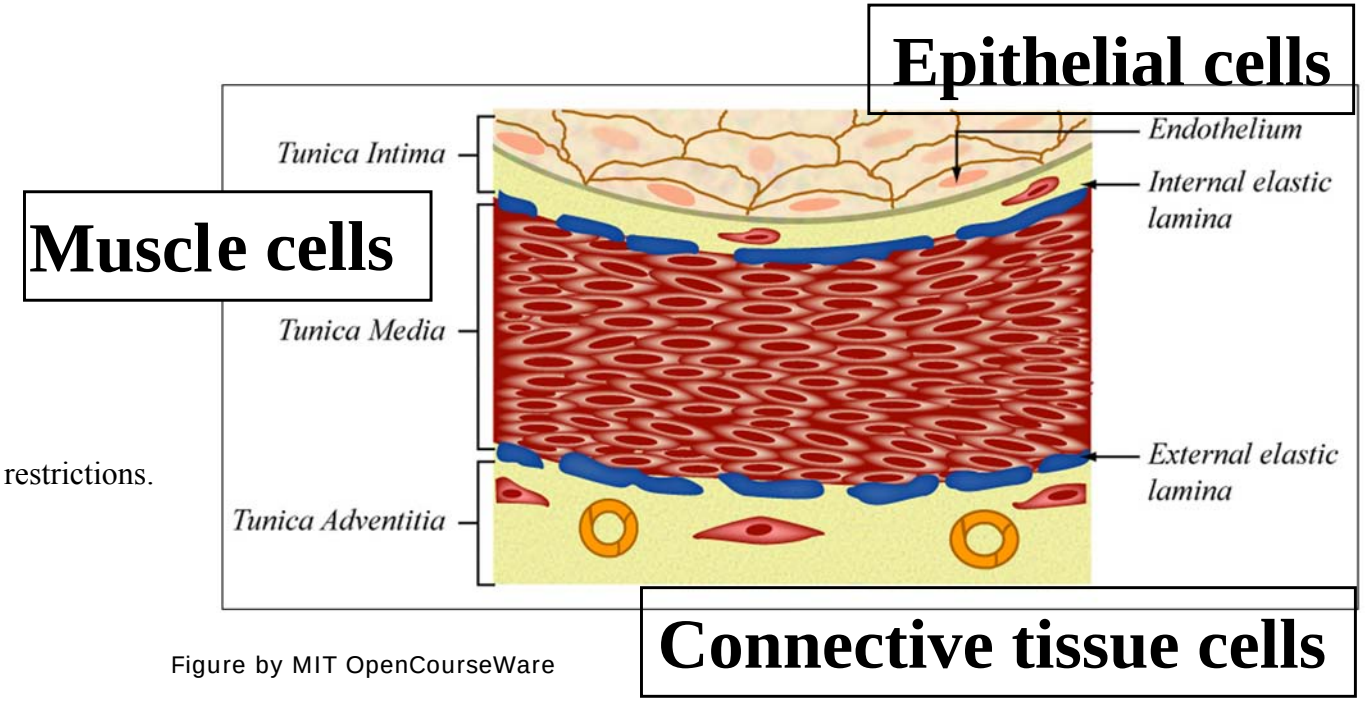


Figure by MIT OpenCourseWare

Netter FH, Heart , The Ciba Collection, 1969

Vein

Artery

Photo removed due to copyright restrictions.

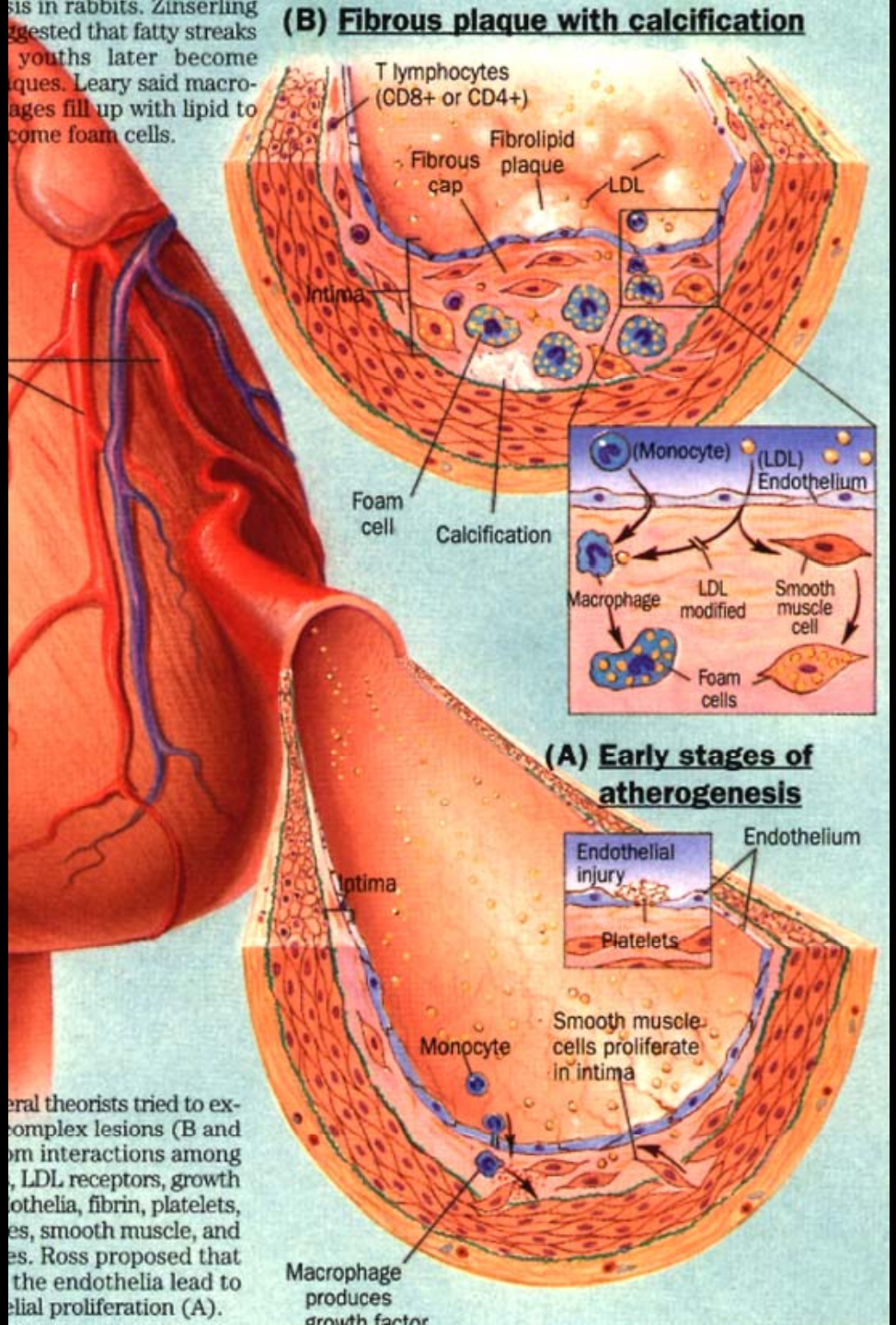
Histology photo comparing vein and artery vascular wall structures.

Normal coronary artery

Lipid deposits in the wall

Two histology photos removed
due to copyright restrictions.

sis in rabbits. Zinserling
gested that fatty streaks
youths later become
ques. Leary said macro-
ages fill up with lipid to
come foam cells.



eral theorists tried to ex-
omplex lesions (B and
om interactions among
, LDL receptors, growth
othelia, fibrin, platelets,
es, smooth muscle, and
es. Ross proposed that
the endothelia lead to
elial proliferation (A).

J NIH 5:100 (1993)

Cardiac Infarct Resulting from Coronary Artery Occlusion

Diagram removed due to copyright restrictions.

Image removed due to copyright restrictions.

Figure 3 in Michaels, A. D., and K. Chatterjee. “Angioplasty Versus Bypass Surgery for Coronary Artery Disease.” *Circulation* 106 (2002): e187-e190. DOI: 10.1161/01.CIR.0000044747.37349.64

F. Schoen

Anastomotic Hyperplasia in an ePTFE Femoropopliteal Graft

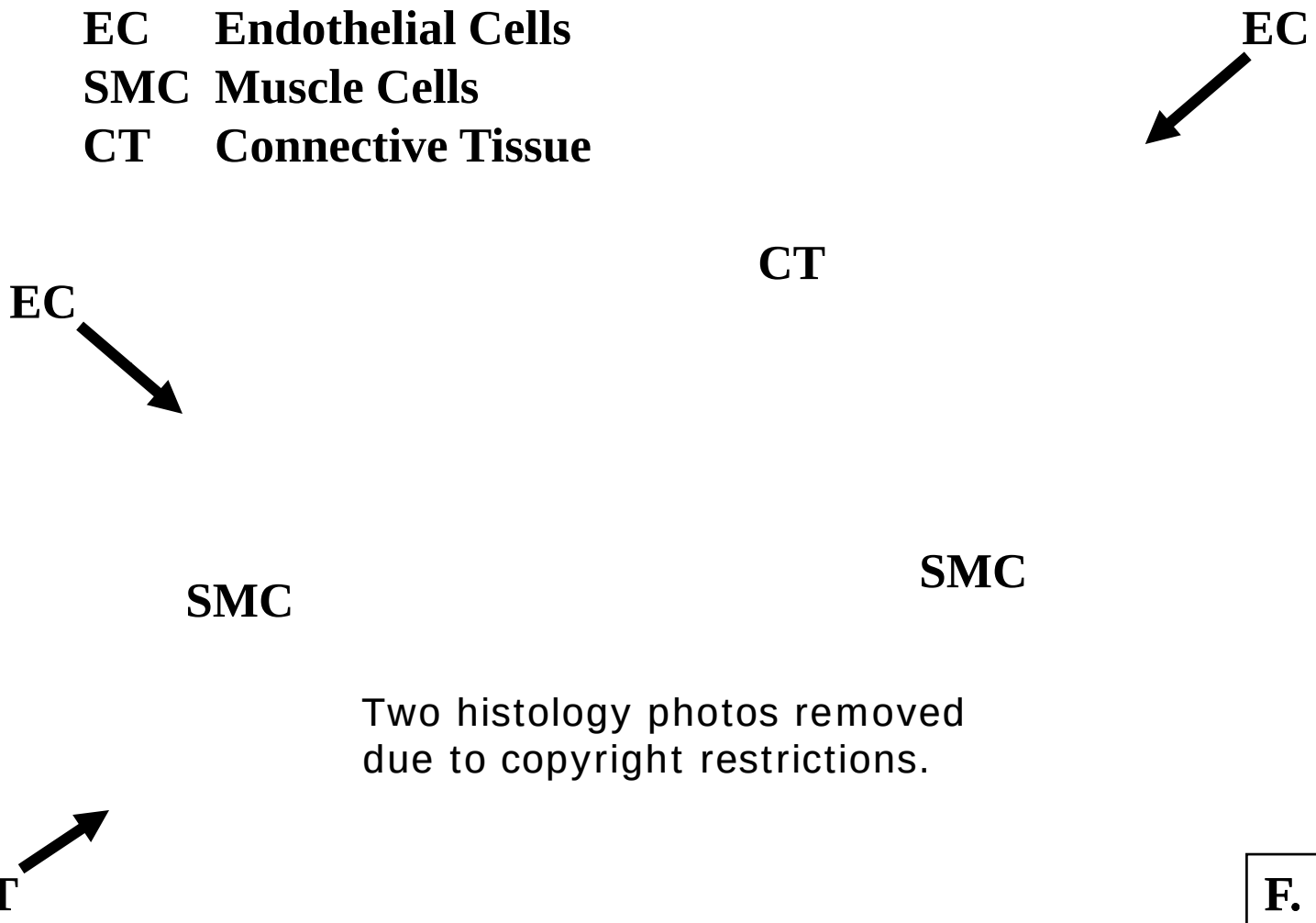
Image removed due to copyright restrictions.

Source: Schoen, F. J, and R. S. Cotran. “Blood Vessels.” In *Pathologic Basis of Disease*, 6th edition. Saunders, 1999. p. 537.

F. Schoen

Vascular Response to Injury: Rabbit Model

EC **Endothelial Cells**
SMC **Muscle Cells**
CT **Connective Tissue**



Two histology photos removed due to copyright restrictions.

F. Schoen

VASCULAR IMPLANTS

- **Permanent artificial vessels**
- **Autografts (saphenous vein)**
- **Tissue engineered blood vessel**

VASCULAR PROSTHESES

Graft Size	Type Used
Large diameter (12-38 mm); Aorta Medium diam. (5-10 mm); Femoral artery Small diam. (< 4 mm); cerebral/coronary	Polyethyleneterephthalate (PET; Dacron) PET, polytetrafluoroethylene (PTFE; Teflon) Vessel autografts; Saphenous vein

- The distinction between large and small diameter vessel replacements is arbitrarily based on the degree of blood compatibility.
- Dacron was introduced into America in 1946 as a polyester polymer of ethylene glycol and terephthalic acid; Polytetrafluoroethylene (Teflon) first became available as a multifilament yarn in 1954.
  - PET and PTFE conduits do not deteriorate after implantation.
  - Strong, nonreactive, noncarcinogenic and tend to retain tensile strength indefinitely.
- Nearly all *large diameter* vascular prostheses are made of Dacron (Bard and Meadox).
  - 75% are bifurcated (replace the lower part of the aorta where it branches into the femoral arteries); 25% are straight.
- 70 % of the *medium diameter* Gore-Tex; 25% Dacron; and 5% biologicals.
- Currently only 1 % of the *small diameter* market is held by synthetic grafts due to lack of blood compatible materials.

http://www.biomed.metu.edu.tr/courses/term_papers/BurcuUnal.htm

Bifurcated Grafts

Photo removed due to copyright restrictions.

Photos of textile vascular prostheses removed due to copyright restrictions.

Hemashield Gold ™ grafts from Boston Scientific.

VASCULAR PROSTHESES
Host Responses

Shortly after a Dacron graft is exposed to arterial blood flow, a predictable sequence of events occurs.

- **Fibrin is absorbed onto the inner graft surface.**
- **In large-diam. prostheses subjected to high volume flow this fibrin layer usually remains thin, typically less than 1 mm.**
- **In smaller-diam. Dacron prostheses in low flow environments, the fibrin layer may increase in thickness, ultimately promoting graft occlusion.**
- **Immediately following implantation the outer lining of the graft is also completely encapsulated with fibrin.**
  - **Organization of the outer fibrinous capsule begins within 2 days.**
  - **Outer layer contains nutrient vessels, middle layer of dense collagen, and an inner layer, in contact with the graft, of organized tissue and foreign body cellular infiltrate.**
  - **Capsule causes a loss of preexisting elasticity(compliance mismatch.**
- **Platelets adhere to the intraluminal fibrin layer and are one of the major constituents of thrombus formed on the surface of a prosthetic conduit.**

VASCULAR PROSTHESES
Complications

- Infection in approximately 2% of synthetic graft.
  - Grafts may become infected by direct inoculation with microbes during the operative procedure, as well as by hematogenous seeding from transient bacteriemias months or years after implantations.
- Structural failures, including aneurysm formation, are rare occurences and are most commonly due to mechanical failures in fabrication.
  - 10 to 20% increase in graft diameter is common following implantation.

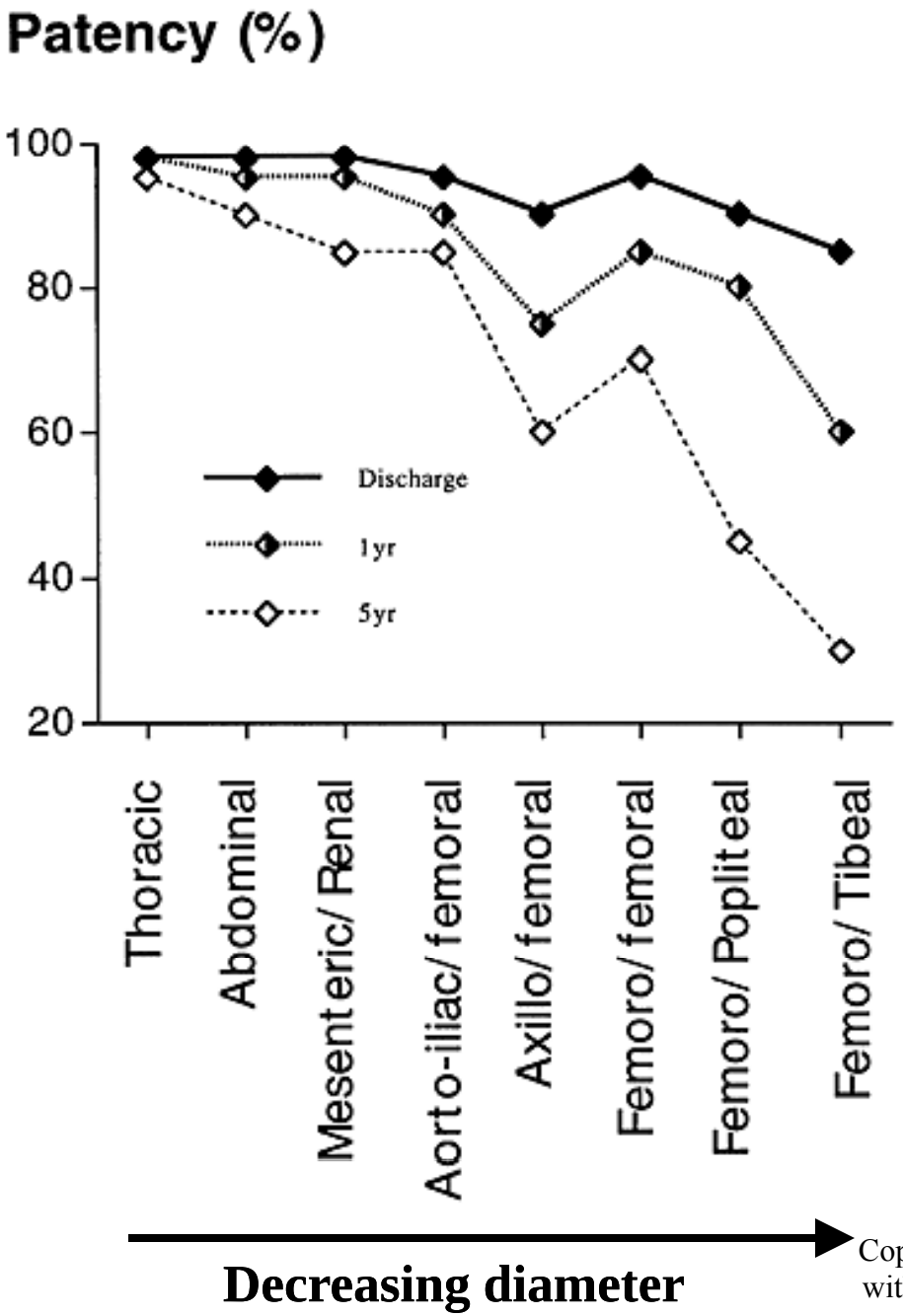
VASCULAR PROSTHESES
Compliance Mismatch

- Prosthetic grafts, once implanted, are not as compliant as indigenous arteries
  - subsequent graft incorporation further hampers compliance.
- Compliance mismatch between graft and artery and the resulting hemodynamic effects at the anastomosis might predispose to intimal hyperplasia, graft thrombosis, or even false aneurysm formation.
- Synthetic elastomers, introduced in 1957, were designed as one solution to problems of compliance mismatch.
  - These conduits simulate the elastic modulus of the artery, giving an elastic response to the graft in both the longitudinal and lateral directions.

VASCULAR PROSTHESES
PRINCIPAL PROBLEMS

Small-caliber (< 10 mm) vessels

- **Occlusion of synthetic prostheses**
- **Morbidity of donor site for autografts**

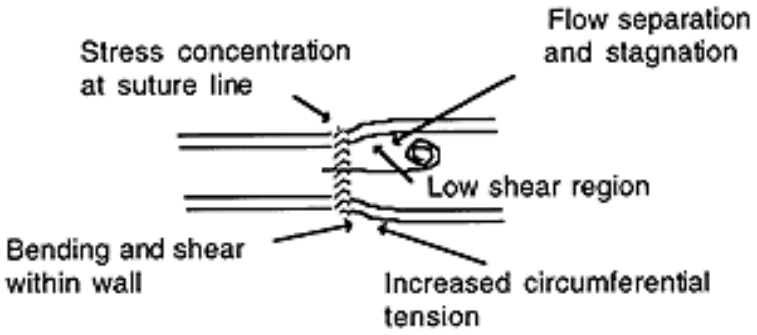


Relationship between patency rate and graft survival time. Grafts with diameter greater than 6 mm have the best survival rates.

S. E. Greenwald, *J Pathol* 190:292;2000 (data from Abbott WM, *et al*. *J Vasc Surg* 1993; 17: 746-756

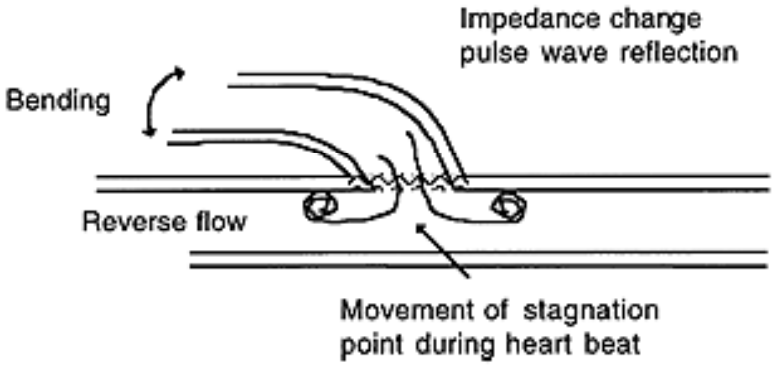
Mechanical environment of the graft anastomosis

End-to-end anastomosis

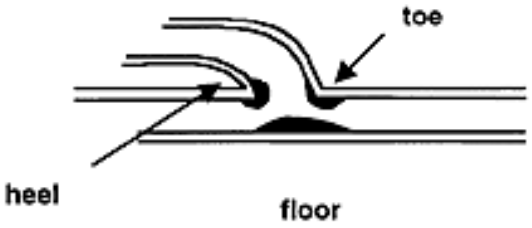


Axial strain ⟷

End-to-side anastomosis



Distribution of intimal hyperplasia



S. E. Greenwald, J Pathol 190:292;2000

HISTORICAL PERSPECTIVE

S. E. Greenwald, J Pathol 190:292;2000

- Large numbers of vascular grafts (excluding valves) used in currently, more than 1 million being inserted each year
  - Majority are grafts or conduits intended to bypass or replace vessels that have become blocked or severely stenosed by disease or trauma.
  - Most are synthetic, but human or animal tissues, denatured in some way, are also used, as are autologous vessels (usually veins).
- The first prostheses were metal, glass or ivory tubes, which rapidly and invariably became blocked by clotted blood.
- Extensive vascular surgery only became possible after the development of a reliable technique for suturing the cut ends of blood vessels in the early years of the 20th century
  - Techniques rapidly improved as a consequence of treating combatants in World War II and Korea.
- Subsequently, human allografts (removed from cadavers and then sterilized) employed to repair damaged arteries.
- The success rate of this procedure was poor, due to the problems of rejection, which were not well understood.

HISTORICAL PERSPECTIVE

S. E. Greenwald, J Pathol 190:292;2000

- In the early phases of the use of prostheses, the establishment of flow without leakage or thrombosis and the survival of flow-dependent tissues were the main objectives.
- As long-term survival of grafted patients became the norm, other problems presented themselves and it became clear that the mechanical and haemodynamic properties of the prosthesis were very significant.

HISTORICAL PERSPECTIVE

S. E. Greenwald, J Pathol 190:292;2000

- By the early 1950s, a number of polymeric materials such as polyethylene and methacrylate had been tried as arterial substitutes in animal experiments
  - it was hoped that their smooth and impermeable surfaces might help to minimize the formation of thrombus.
- In 1952, Vorhees *et al.* reported that a silk suture exposed for several months to flowing blood in the right ventricle became covered by a glistening film of tissue free of microscopic thrombi and this observation inspired the idea that a woven rather than a smooth material
  - by stimulating the formation of this layer, would provide a non-thrombogenic surface suitable for an arterial prosthesis.
- Blakemore and Vorhees described the first clinical use of this fabric as an arterial prosthesis and showed that all detectable leakage of blood through the weave had ceased within 1 min after the prosthesis was filled with blood at arterial pressure.

HISTORICAL PERSPECTIVE

S. E. Greenwald, J Pathol 190:292;2000

- Once the idea of porous woven fabrics was introduced, a variety of materials including nylon, Teflon, Orlon, Dacron, and polyurethane were tested.
  - Nylon was soon abandoned because it was found to degenerate rapidly following implantation.
- Early clinical comparisons of graft success suggested that Dacron was the most promising material.
  - Although Dacron (polyethylene terephthalate) is still widely used as a graft material (it remains the most widely used for aortic and iliac grafts), in the last 25 years a number of other compounds have been developed, the most important being expanded polytetrafluoroethylene (PTFE) and polyurethane.

Scanning Electron Micrographs

Mersilene Dacron Mesh: 1,000 um scale.

Teflon Mesh: 1,000 um scale

Photos removed due to copyright restrictions.

Gore-Tex : 10 um scale.

Marlex Polypropylene Mesh: 1,000 um scale.

HISTORICAL PERSPECTIVE

S. E. Greenwald, J Pathol 190:292;2000

The physical and mechanical properties of commercially available grafts vary widely, but a number of characteristics common to all successful vascular prostheses may be identified.

- **biocompatibility**
- **lack of chemical reactivity**
- **very low thrombogenicity**
- **porosity; the prosthesis should allow the leakage of a small amount of blood. This leads to a tightly adherent thrombus, permitting its subsequent replacement by fibrin and fibrous tissue. The end result of this process is the formation of a non-thrombogenic surface resembling that of the native vessel.**
- **sterility**
- **no leaching of chemicals used in the manufacturing process; there should be a long-term ability to resist the elution of these chemicals.**

HISTORICAL PERSPECTIVE

S. E. Greenwald, J Pathol 190:292;2000

The physical properties essential for simple insertion and long-term success of a graft include:

- **flexibility**
- **the ability to resist kinking and squashing**
- **the ability to stretch**
- **availability in a range of sizes to match the dimensions of the native vessels**
- **tensile and shear strength sufficient to resist fraying at cut edges and tearing out of sutures**
- **circumferential strength sufficient to withstand arterial pressures**
- **mechanical properties approximate to those of the native vessels to which they are attached.**

HISTORICAL PERSPECTIVE

S. E. Greenwald, J Pathol 190:292;2000

- Many of these requirements for a vascular graft, except the matching of mechanical properties, are provided by modern materials
  - the success rate of the implantation procedure and the long-term patency of large grafts (those with a diameter greater than 6 mm) is high and continues to improve.
- The materials of choice for small grafts are autologous blood vessels such as saphenous vein or, for coronary artery grafting, the internal mammary artery.
  - However, in at least 30% of patients the saphenous or other veins cannot be used, due to pre-existing disease or previous use.

HISTORICAL PERSPECTIVE

S. E. Greenwald, J Pathol 190:292;2000

- The major causes of failure in the short term include:
  - infection
  - haemorrhage
    tearing at the suture line
  - failure of the graft material itself
- The long-term success rate of grafts with a diameter of less than 6 mm is far from satisfactory and falls steadily as the diameter becomes smaller
- The most common cause of long-term failure in these small grafts is **intimal hyperplasia** at the anastomotic site
  - proliferation and migration of vascular smooth muscle cells from the media to the intima
  - subsequent synthesis of matrix proteins and other extracellular material
- Intimal hyperplasia in vascular grafts is still poorly understood, but its development is strongly associated with disturbed blood flow and further injury to the vessel wall

VASCULAR PROSTHESES
TISSUE RESPONSE

- **Thrombosis; Pseudointimal Hyperplasia**
- **Neointimal Hyperplasia**

Natural Vessel

Set of three diagrams removed due to copyright restrictions.

Neointima

Biomaterial

Pseudointima

F. Schoen, 1989

VASCULAR PROSTHESES TISSUE RESPONSE

- **Thrombosis; "pseudointimal hyperplasia"**
  - **Blood clot formation on the intimal surface**
  - **Fibrin, platelet debris, red blood cells**
  - **Forms within 24 hours of implantation**
  - **Problem: thrombus formation and contribution to neointimal thickening and occlusion**
  - **Solution: prevent adherence and activation of platelets; patients must remain on anti-coagulant therapies**

Image removed due to copyright restrictions.
See Fig. 10.2, “The role of platelets in thrombosis.”
In Rubin, E., and H. M. Reisner, editors. *Essentials of Rubin’s Pathology*. Lippincott Williams & Wilkins, 2008.

http://books.google.com/books?id=7HdzBBhtxycC&pg=PA197

VASCULAR PROSTHESES TISSUE RESPONSE

- **Neointimal Hyperplasia**
  - **Tissue growth onto the surface from the anastomoses**
  - **Smooth muscle and endothelial cells migrate from the artery into the graft and proliferate under the influence of various cytokines (also referred to as pannus and fibromuscular hyperplasia)**
  - **Pannus advances at the rate of 0.1 mm/wk**
  - **Never covers the entire surface in humans; max. 1-2 cm**

VASCULAR PROSTHESES
TISSUE RESPONSE

- **Neointimal Hyperplasia**
  - **Problem: intimal thickening and occlusion**
  - **Solution: reduce thrombosis or cell proliferation**

VASCULAR PROSTHESES TISSUE RESPONSE

- **Neointimal Hyperplasia; Other Contributing Factors**
  - **Compliance mismatch; the prosthesis is stiffer than the natural artery, at the junction**
  - **Hemodynamic shear stress; elevated shear stress inhibits smooth muscle cell proliferation and neointimal thickening (in porous PTFE grafts in baboons); wall shear stress primarily determined by the prosthesis diameter**

MECHANICAL FACTORS

S. E. Greenwald, J Pathol 190:292;2000

A complete description of the elastic properties of the arterial wall or of a graft must take into account the following phenomena:

- anisotropy: different physical properties in the radial, circumferential, and longitudinal directions
- viscoelasticity: the stiffness of the vessel depends on the rate at which it is deformed
- the non-linear stress-strain relationship - a consequence of the fact that blood vessels are composed of several materials, each with different elastic properties
- the presence of residual stresses - the forces that remain within the vessel wall when all external loads have been removed.

Compliance of Natural and Artificial Materials for Vascular Prostheses

Material	Compliance % per mmHg×10^{-2}
Human femoral artery	6.0
Human saphenous vein	4.6
Glutaraldehyde-treated umbilical vein	3.9
Denatured bovine carotid	2.9
Dacron	2.0
PTFE	1.5

* Data from *in vitro* measurements.

R. Walden, *Arch Surg* 1980; 115: 1166-1169

COMPLIANCE MISMATCH

S. E. Greenwald, J Pathol 190:292;2000

- Realizing that most vascular prostheses are much stiffer than the arteries to which they are attached, Gozna and others suggested that the elastic properties of a vascular graft may be important in determining its effectiveness, especially in the long term.
- This notion soon became widely accepted, although there are very few well-controlled studies that demonstrate a clear association between improved long-term graft performance (as measured by patency rates) and close matching of graft and artery elastic properties.
- Grafts with a diameter of more than 6 mm are mostly made of Dacron, which is at least three times stiffer than a typical large artery and in those grafts, the 5-year patency rate approaches 100%.
- However, the majority of the smallest grafts fail within 5 years and of these, most do so because the vessel immediately downstream of the graft becomes blocked due to intimal hyperplasia

COMPLIANCE MISMATCH

S. E. Greenwald, J Pathol 190:292;2000

- During the last 25 years, most attempts to test the hypothesis that the failure of small grafts is due to compliance mismatch have taken either a functional approach, in which the patency rates of stiff grafts have been compared with those of more compliant grafts placed in a similar environment, or an experimental approach, in which a mechanism for the known association between small grafts and intimal hyperplasia is sought.
- Many of the functional studies are handicapped by the problem of poor controls.
  - the possibility that the different rates of failure are due to differences in surface properties, wall thickness, the ability to resist tearing, etc. rather than compliance cannot easily be dismissed.
- Walden *et al*.reported a striking correlation between the compliance of femoro-popliteal grafts in man and the fraction remaining patent after 2 years.
  - However, as the authors themselves point out, these differences in compliance (measured *in vitro* under static conditions) were achieved by using a range of disparate materials with different surface properties, different degrees of biocompatibility, and a differing tendency to become stiffer during the time that they are implanted as the material becomes invested with thrombus and fibrous tissue.

OTHER MECHANICAL FACTORS

S. E. Greenwald, J Pathol 190:292;2000

- Other mechanical factors which are thought to stimulate the formation of intimal hyperplasia are
  - suture line stress, in which distortions in the native vessel due to the holes formed by the sutures as well as the tension due to their presence cause concentrations of force
  - increased circumferential tension in the vessel wall adjacent to the anastomosis.
- It has also been suggested that bending in the region of the anastomosis due to the different degrees of pulsatile strain resulting from compliance mismatch may contribute to the formation of intimal hyperplasia.
  - However, the radial movement due to a pulse pressure of 20 mmHg of a femoral artery with a diameter of 4 mm and compliance of the order of 0.13%/mmHg would be less than 0.03 mm (i.e. less than 1% of the diameter) and that of a PTFE graft would be approximately one-third of this.
  - It is questionable, therefore, whether such a small degree of bending would cause an injury comparable to that due to the suture itself

Improving Vascular Grafts: The Importance of Mechanical and Haemodynamic Properties

Summary

- In the last 40 years, the success rate of vascular prostheses with a diameter greater than 6mm has risen steadily
  - 5-year survival rates exceeding 95% in most centres
- With smaller grafts no comparable improvement has occurred
  - the majority failing within 5 years
  - failure due to intimal hyperplasia and, ultimately atherosclerosis
  - failure in and around the downstream anastomosis
- Clinical evidence suggests that the patency rates of small grafts are improved by matching the elastic properties of the graft to that of the artery into which it is placed.

S. E. Greenwald, J Pathol 190:292;2000

Improving Vascular Grafts: The Importance of Mechanical and Haemodynamic Properties

- Although there is little reliable evidence that elastic mismatch *per se* is the cause of intimal hyperplasia, it is generally accepted that mechanical factors, including the following, are important in its genesis.
  - disturbed flow at the anastomosis leading to fluctuations in shear stress at the endothelium (a known cause of intimal hyperplasia in normal arteries)
  - injury due to suturing
    stress concentration at the anastomosis.
- Few suitable materials or techniques have yet been developed to improve the long-term survival rates of small grafts.
- Recent advances in tissue engineering in which prostheses are manufactured by culturing vascular smooth muscle cells on a tubular scaffold of biodegradable polymer may ultimately make it possible to manufacture biologically and haemodynamically compatible grafts with diameters as small as 1mm.

S. E. Greenwald, J Pathol 190:292;2000

VASCULAR IMPLANTS

- **Permanent artificial vessels**
- **Autografts (saphenous vein)**
- **Tissue engineered blood vessel**

Cell-Seeded Prostheses
Vascular Tissue Engineering

Diagram removed due to
copyright restrictions.

Diagram removed due to copyright restrictions.
Drawings of vascular implant in flat (unrolled) and rolled forms.

D Seliktar and R Nerem

Functional Arteries Grown in Vitro

L. E. Niklason, *et al.* Science 284:489;1999

- Atherosclerotic vascular disease, in the form of coronary artery and peripheral vascular disease, is the largest cause of mortality in the United States.
- Surgical mainstays of therapy for affected vessels less than 6 mm in diameter include bypass grafting with autologous veins or arteries
  - however, adequate tissue for bypass conduits is lacking in many patients.
- Artificial materials, when used to bypass arteries that are less than 6 mm in diameter, have thrombosis rates greater than 40% after 6 months.
- Although novel approaches for producing small-caliber arterial grafts have been developed, problems with mechanical properties or the utilization of neonatal cells have heretofore prevented clinical implementation.

Functional Arteries Grown in Vitro

L. E. Niklason, *et al.* Science 284:489;1999

- A tissue engineering approach was developed to produce arbitrary lengths of vascular graft material from smooth muscle and endothelial cells derived from a biopsy of vascular tissue.
- Bovine vessels cultured under pulsatile conditions
  - rupture strengths greater than 2000 millimeters of mercury
  - suture retention strengths of up to 90 grams
  - collagen contents of up to 50 percent
- Cultured vessels showed contractile responses to pharmacological agents
- Smooth muscle cells displayed markers of differentiation
  - calponin and myosin heavy chains
- Tissue-engineered arteries implanted in miniature swine
  - patency documented up to 24 days by digital angiography

Functional Arteries Grown in Vitro

L. E. Niklason, *et al.* Science 284:489;1999

- Suspension of cultured SMCs isolated from the medial layer of bovine aorta was pipeted onto tubular biodegradable polyglycolic acid (PGA) scaffolds that were secured in bioreactors.
- The surface of the PGA scaffolds was chemically modified with sodium hydroxide, which caused ester hydrolysis on the surface of the fibers, leading to increased hydrophilicity, increased adsorption of serum proteins, and improved SMC attachment.
- After an initial SMC seeding period of 30 min, the bioreactors were filled with medium and the SMCs were cultured under conditions of pulsatile radial stress for 8 weeks.
- To produce an endothelial layer, an EC suspension of 3 million cells/ml was injected into the lumen.
- Control vessels were cultured without pulsatile radial stress under otherwise identical conditions.

Pulsatile “Bioreactor” for Vascular Tissue Engineering

Several slides with images from the article removed due to copyright restrictions.

L. E. Niklason, *et al.* Science 284:489;1999

Vessel type*	Wall thickness (cm)	Collagen (% dry weight)	Suture retention (g)	SMC density (10^8 cells/ml)
5 P	0.019 ± 0.006	29 ± 6	40 ± 16	0.40 ± 0.16
	(*n* = 4)	(*n* = 4)	(*n* = 4)	(*n* = 4)
	†		(*P* < 0.001)	†
5 NP	0.009	–	2.7 ± 1.2	–
	(*n* = 1)		(*n* = 3)	
8 P	0.038 ± 0.004	50 ± 5	91 ± 26	0.93 ± 0.37
	(*n* = 5)	(*n* = 6)	(*n* = 6)	(*n* = 5)
		(*P* < 0.005)	(*P* < 0.005)	
8 NP	0.023 ± 0.004	35 ± 3	22 ± 8	1.19 ± 0.14
	(*n* = 3)	(*n* = 4)	(*n* = 6)	(*n* = 3)
Native	0.029 (18)	45 ± 9–	273 ± 31–	2.87 ± 0.14§
		‡	‡	

* P, pulsed; NP, nonpulsed; number represents weeks.

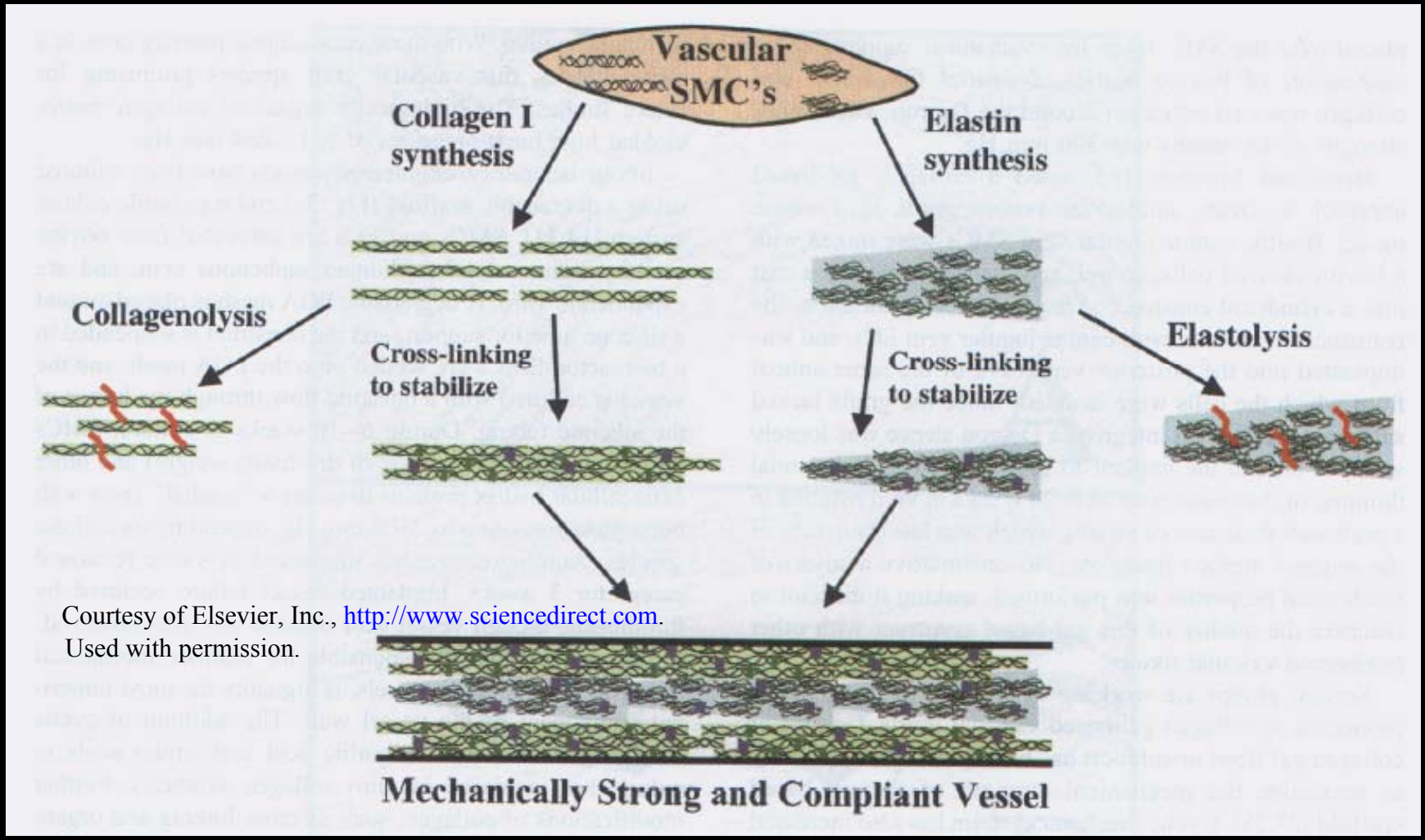
– Data insufficient.

‡ Measured from bovine muscular arteries stripped of adventitia.

§ Measured from bovine arteries by fluorometric assay.

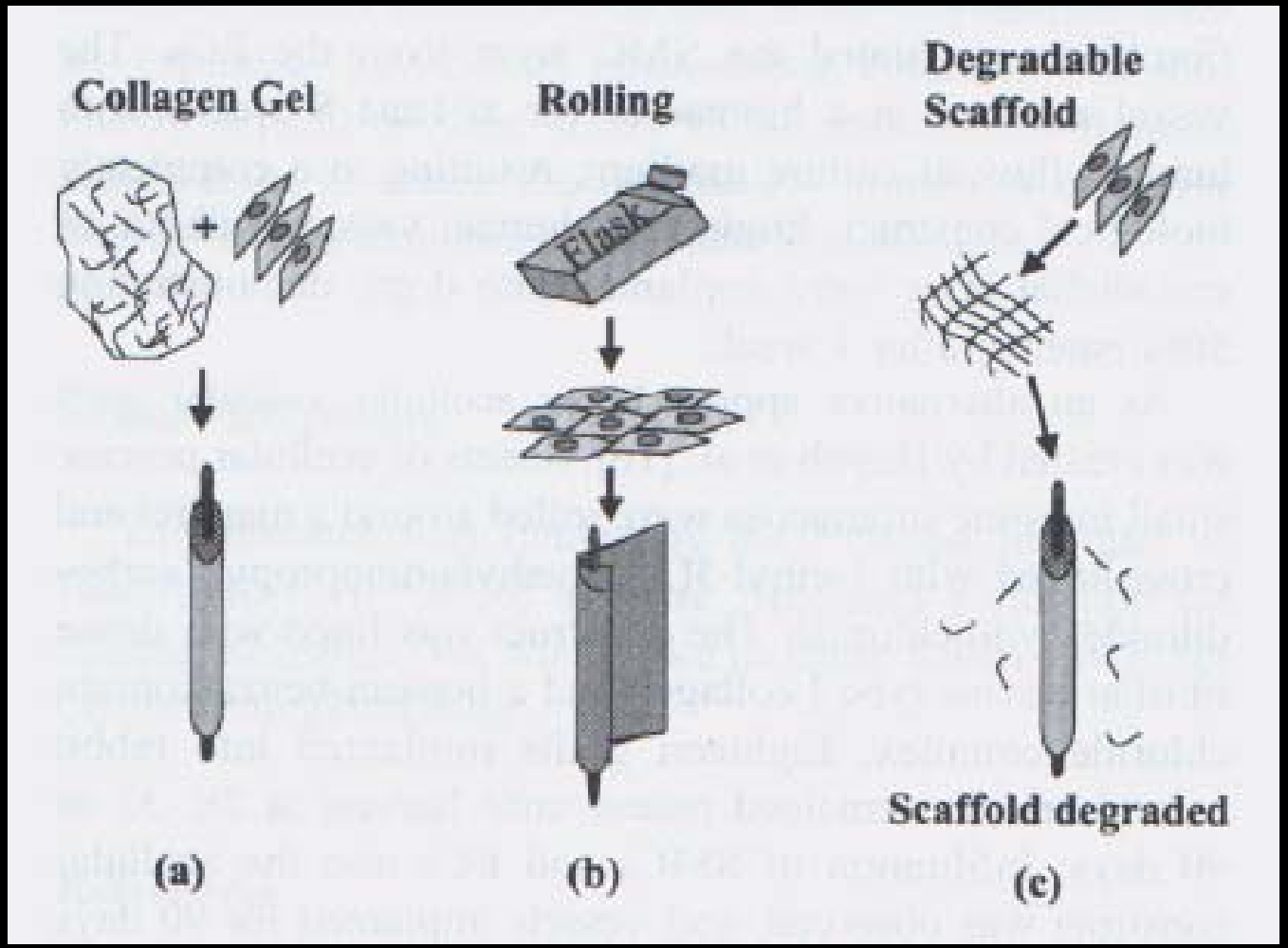
Requirement for Growing Tissue-Engineered Vascular Grafts

SL Mitchell, Cardiovasc. Path. 12:59 (2003)



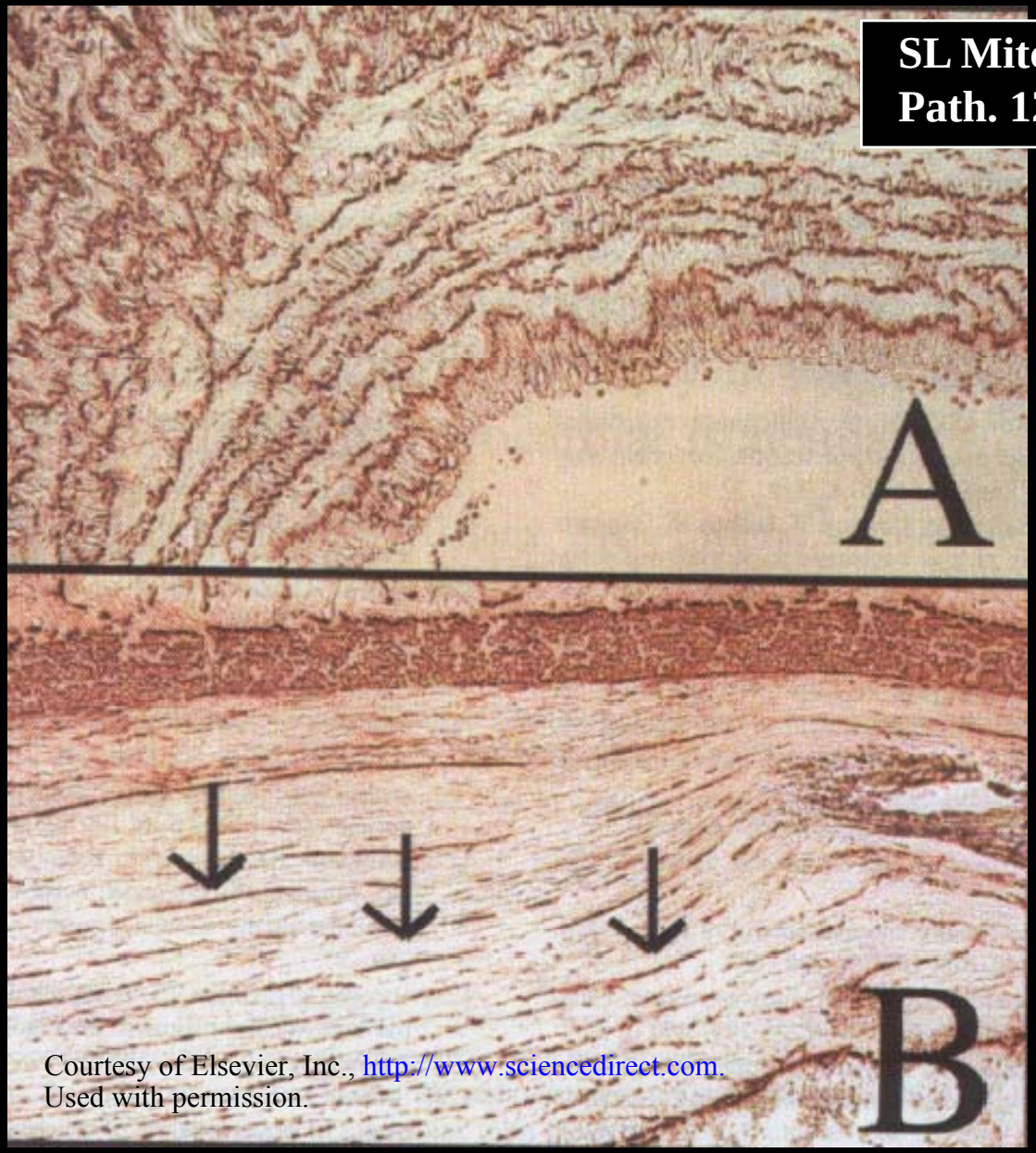
Collagen and elastin are excreted by smooth muscle cells. Cross-linking stabilizes collagen and elastin, making them less suseptible to proteolysis. Well-organized layers of insoluble collagen and elastin result in a strong, compliant vessel.

SL Mitchell, Cardiovasc. Path. 12:59 (2003)



Development of (a) collagen gel-based, (b) rolled sheet, and (c) degradable scaffold vascular grafts.

SL Mitchell, Cardiovasc. Path. 12:59 (2003)



Elastin immunostaining (arrows) in a native (A) and an explanted tissue-engineered artery (B).

Bursting Strength of Tissue-Engineered Blood Vessel (TEBV; EN, collagen sheet, SMC,FB)

Two graphs removed due to copyright restrictions.

IM: inner membrane, collagen
HSV: human saphenous vein

N L'Heureux, *et al*, FASEB J 12:47;1998

20.441J / 2.79J / 3.96J / HST.522J Biomaterials-Tissue Interactions
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