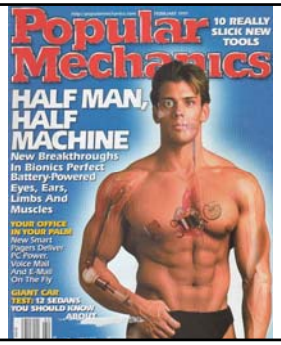
Biomedical Polymers & Biocompatibility

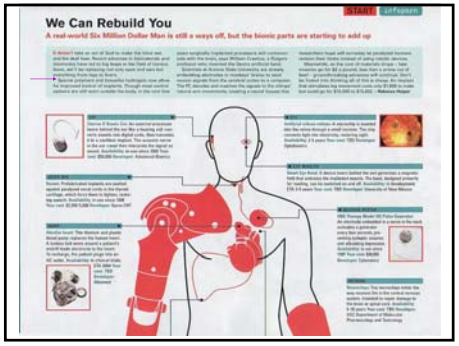
Taken to extremes. Star Trek's half-machine, half-human Borg featured biosensors run riot.

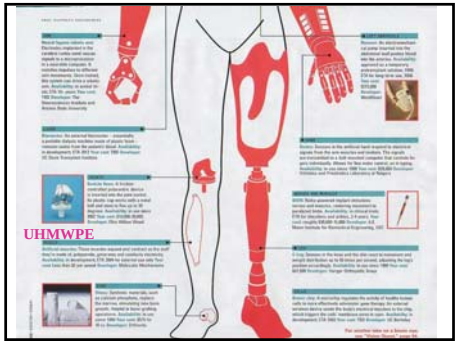
- Artificial skin
- Bone-grafting material
- Blood vessels
- Cornea
- Stem cell transplants

TERMINATOR
LIQUID METAL
LIQUID PLASTICS



We can rebuild him. We have the technology.
We have the capability to make the world's first Bionic man. Steve Austin will be that man. Better than he was before.
Better . . . stronger . . . faster.





BIOMATERIALS AND BIOCOMPATIBILITY

Biomaterials are basically any non-viable materials which become a part of the body either temporarily or permanently to restore, augment, or replace the natural functions of the living tissues or organs in the body (1). Biomaterials have been used for various applications such as prosthetic, diagnostic, and therapeutic applications. Many controlled drug delivery systems, especially implantable systems, are also biomaterials. Recently, a variety of drugs have been incorporated into implantable biomaterials to improve the functions of the biomaterials. For example, antibiotics or growth hormone was incorporated into implantable biomaterials for delivery at the implant interface to prevent deep-wound sepsis or to improve wound healing and tissue repair (2).

When biomaterials are placed inside the body, they are expected to perform with a desirable host response in a specific application without any side effects, such as toxic, carcinogenic, immunologic and inflammatory responses. Biocompatibility is the appropriate biological performance, either local or systemic, of a given implant in a specific application (3). Appropriate host response varies depending on the type of materials implanted and their intended use (4). Thus, the desirable host response may be total inertness and no interaction with tissues surrounding the implanted materials or positive interaction resulting in active participation of the cells surrounding the materials. Biocompatibility is a dynamic two-way process that involves the time-dependent effects of the host on the material and the material on the host (5). No clear, absolute definition of biocompatibility exists yet mainly due to the fact that the biomaterials area is still evolving. Simply put, however, the performance of a biomaterial, if biocompatible, should not be affected by the host and the host should not be negatively affected by the implanted biomaterials.

BIOMATERIALS SCIENCE

An Introduction to Materials in Medicine 2nd Edition

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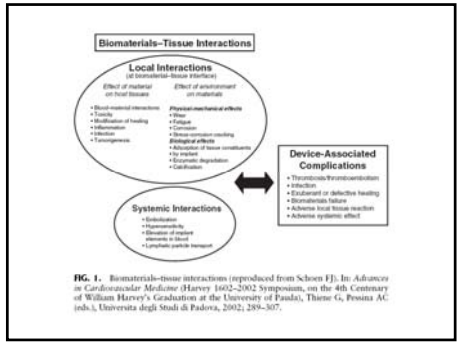


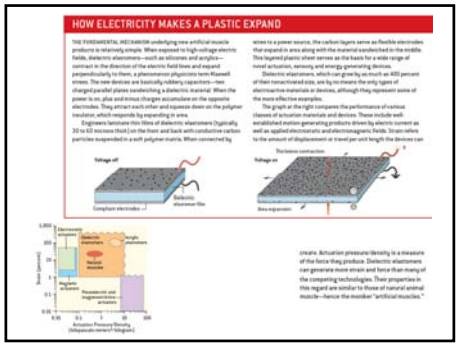
FIG. 1. Biomaterials–tissue interactions (reproduced from Schoen FJ). In: *Advances in Cardiovascular Medicine* (Harvey 1602–2002 Symposium, on the 4th Centenary of William Harvey's Graduation at the University of Pauda), Thiene G, Pessina AC (eds.), Universita degli Studi di Padova, 2002; 289–307.

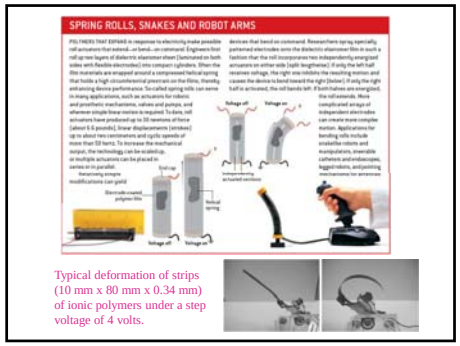
EXAMPLES OF BIOMATERIALS

1. Artificial heart
2. Prosthetic cardiac valves
3. Cardiac pacemakers
4. Vascular graft (sortofluorocarbon grafts)
5. Blood oxygenator
6. Extracorporeal dialysis (for acute and chronic renal failure).
7. Blood circulation tubing
8. Intravascular catheter
9. Urinary catheter
10. Peritoneal dialysis catheters
11. Cerebrospinal fluid shunts
12. Suture
13. Contact lens
14. Intraocular lens
15. Artificial skin
16. Burn dressing
17. Prosthetic joints
18. Endotracheal tubes
19. Intrauterine contraceptive devices
20. Implantable drug delivery devices

Biomaterials

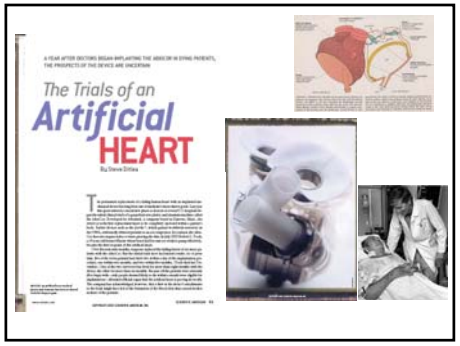
REPLACEMENT ARM AND HAND will someday be fabricated of artificial tissues. The structure of each system—muscle, bone, blood vessels, skin and so on—would be duplicated in biodegradable plastic. These "scaffolds" would then be seeded with cells of the relevant tissue. The cells divide, and the plastic degrades; finally, only coherent tissue remains. A mechanical pump would provide nutrients and remove wastes until the arm, which would take roughly six weeks to grow, can be attached to the body. Most of this technology is already in place. The remaining hurdle is regeneration of nerve tissue. (Depiction of a gradient of formation is for illustrative purposes; all the tissue would in fact form at the same time.)

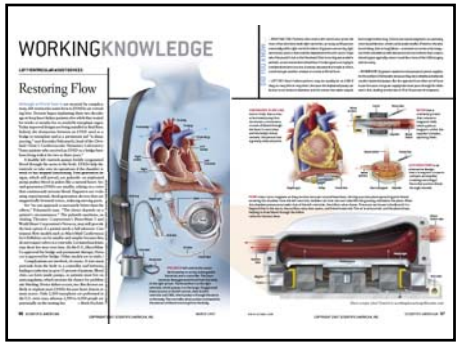


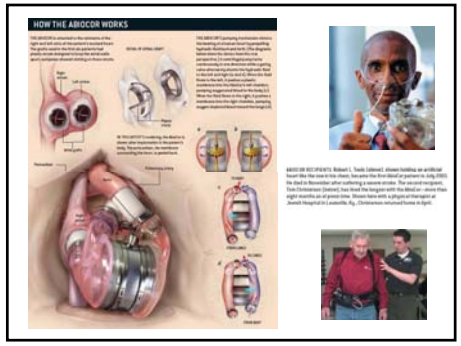


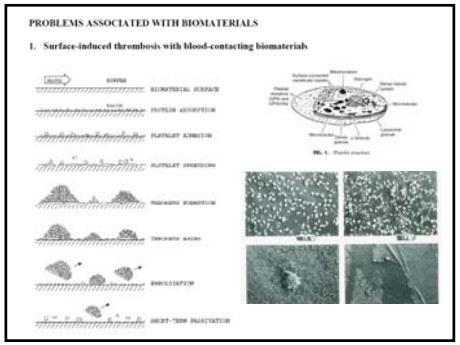
Typical deformation of strips (10 mm x 80 mm x 0.34 mm) of ionic polymers under a step voltage of 4 volts.

Blood-Contacting Biomaterials









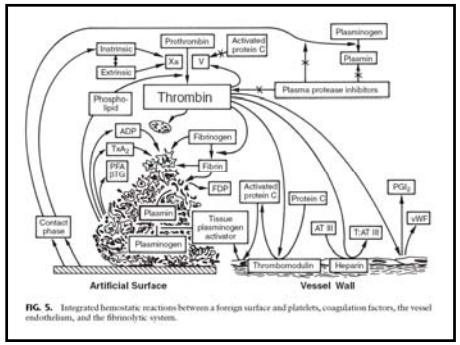
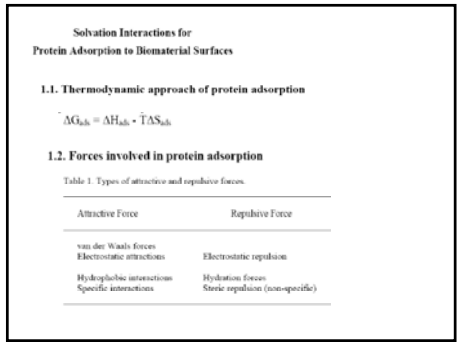


FIG. 5. Integrated hemostatic reactions between a foreign surface and platelets, coagulation factors, the vessel endothelium, and the fibrinolytic system.



Solvation Interactions for Protein Adsorption to Biomaterial Surfaces

1.1. Thermodynamic approach of protein adsorption

$$\Delta G_{ads} = \Delta H_{ads} - T\Delta S_{ads}$$

1.2. Forces involved in protein adsorption

Table 1. Types of attractive and repulsive forces.

Attractive Force	Repulsive Force
van der Waals forces Electrostatic attractions	Electrostatic repulsion
Hydrophobic interactions Specific interactions	Hydration forces Steric repulsion (non-specific)

2. BASIC CONCEPTS OF SOLVATION INTERACTIONS

2.1. Water structuring

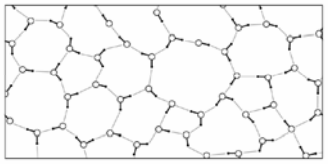


Fig. 1. Artistic description of structuring of bulk water.

2.2. Hydration forces

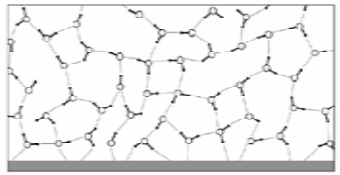


Fig. 2. Water structuring on hydrophilic surface. Water molecules can participate in the formation of networked water structure.

2.3. Hydrophobic interactions

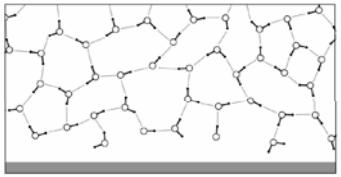


Fig. 3. Water structuring on hydrophobic surface. Water molecules cannot participate in self-association of water molecules near the surface.

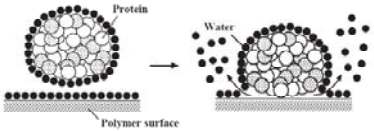


Fig. 4. Schematic description of protein adsorption on the polymer surface. Water molecules are removed from contact sites between amino acid residues and the polymer surface. Some of water molecules remain trapped in certain spaces between the protein and the surface if void sizes are larger than water molecules. From reference (35).

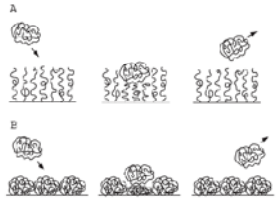
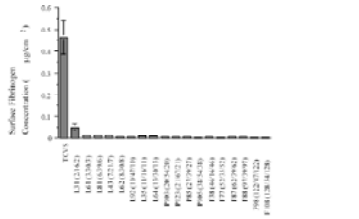


Fig. 2. Schematic description of steric repulsion exerted by the surface-grafted linear polymers such as poly(ethylene oxide) (A) and globular proteins such as albumin (B).

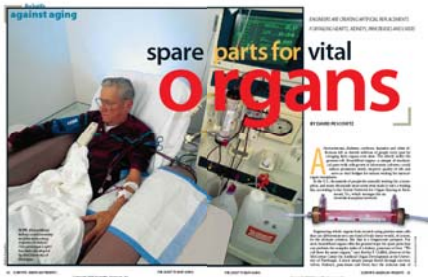
Pluronics® are PEO-poly(propylene)-PEO (PEO-PPO-PEO) triblock copolymers



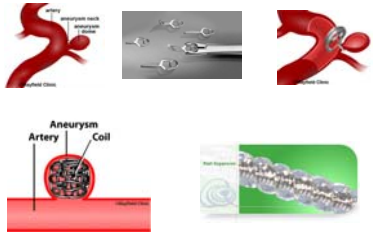
Polymer used in surface grafting

Fig. 5. Fibrinogen adsorption to glass surfaces grafted with various Pluronic® surfactants (L, P, and F series). The control surface was trichlorovinylsilane-modified glass (TCVS). The three numbers in parentheses indicate the numbers of repeating units of ethylene oxide (EO) and propylene oxide (PO) in the poly(EO)/poly(PO)/poly(EO). From reference (86).

(Clotting is Harmful)



Aneurysm Treatment (Clotting is Beneficial)

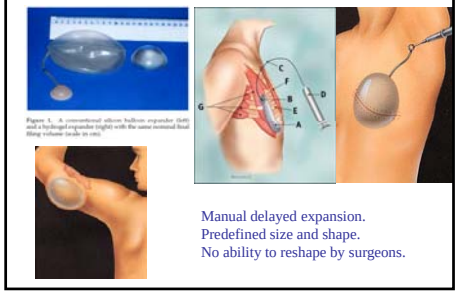


HydroCoil Embolic System: MicroVention (www.microvent.com/Home/hydrocoil/index.html)

http://www.nlm.nih.gov/medlineplus/ency/imagepages/19243.htm

The procedure called gastroscopy involves the placing of an endoscope (a small flexible tube with a camera and light) into the stomach and duodenum to search for abnormalities. Tissue samples may be obtained to check for H. pylori bacteria, a cause of many peptic ulcers. An actively bleeding ulcer may also be cauterized (blood vessels are sealed with a burning tool) during a gastroscopy procedure

Tissue Expander



Manual delayed expansion.
Predefined size and shape.
No ability to reshape by surgeons.

Current Tissue Expanders: Hydrogels

http://www.osmed.biz/html_s/produkte/produkte.html

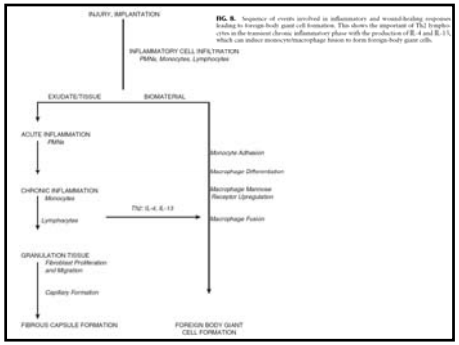
Copolymers of methylmethacrylate and N-vinylpyrrolidone

The volume increase of 3-12 folds.

Hydrogel in silicone shell to reduce the swelling speed.

Predefined size and shape.
No ability to reshape by surgeons.

Silicone Gel Breast Implants



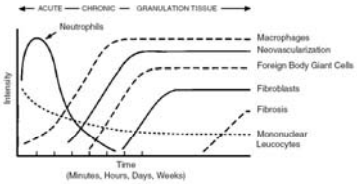


FIG. 1. The temporal variation in the acute inflammatory response, chronic inflammatory response, granulation tissue development, and foreign-body reaction to implanted biomaterials. The intensity and time variables are dependent upon the extent of injury created in the implantation and the size, shape, topography, and chemical and physical properties of the biomaterial.

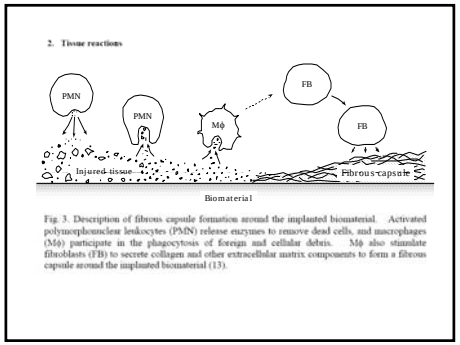
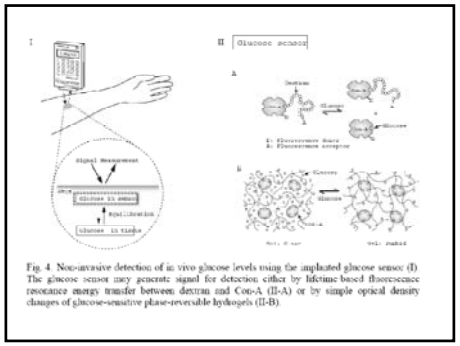


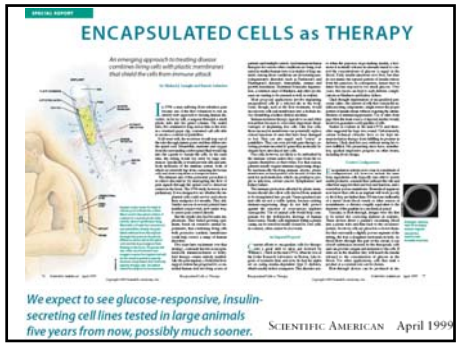
Fig. 3. Description of fibrous capsule formation around the implanted biomaterial. Activated polymorphonuclear leukocytes (PMN) release enzymes to remove dead cells, and macrophages (Mϕ) participate in the phagocytosis of foreign and cellular debris. Mϕ also stimulate fibroblasts (FB) to secrete collagen and other extracellular matrix components to form a fibrous capsule around the implanted biomaterial (13).

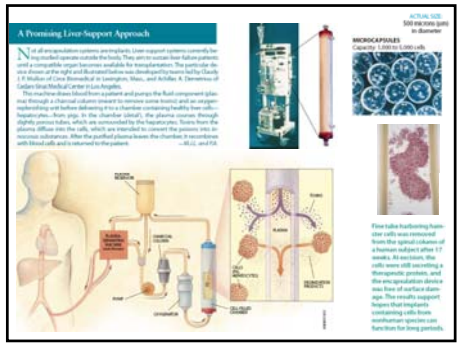
Continuous Glucose Monitoring and Insulin Delivery

Records glucose levels every five minutes.
Replace the sensor after three days of use.
Required to take fingersticks twice a day order to calibrate the glucose sensor.

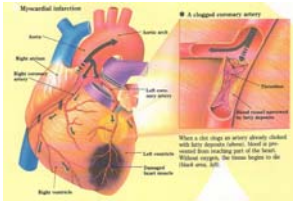
Sensor-Augmented System

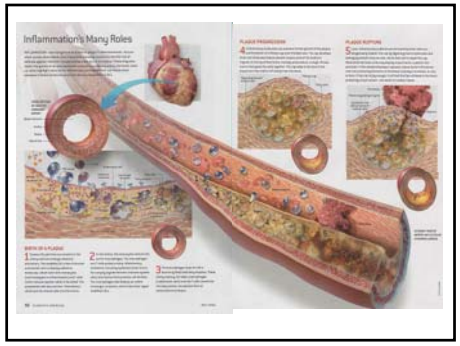




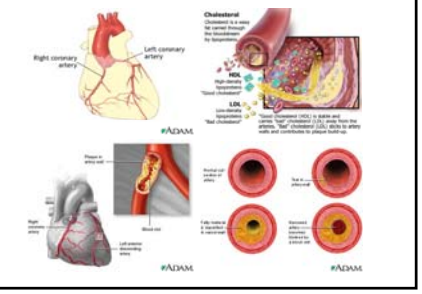


Drug-Eluting Stents:
An Example of Biomaterial-Drug Combination Product

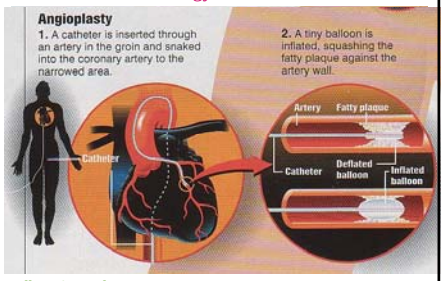




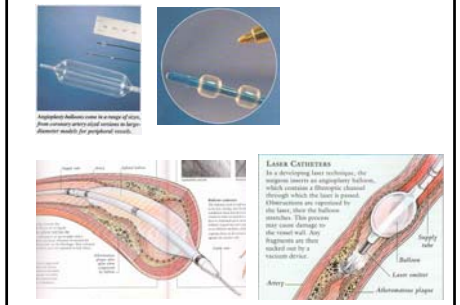
Atherosclerosis



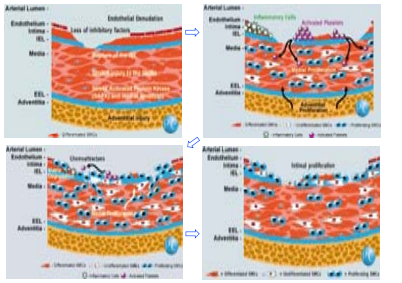
Interventional Cardiology



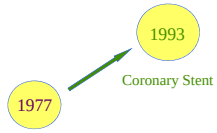
Balloon Angioplasty Percutaneous Transluminal Coronary 1977



Restenosis Cycle



Interventional Cardiology

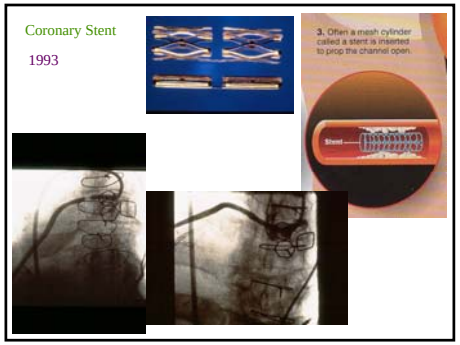


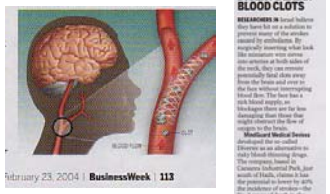
Balloon Angioplasty

Percutaneous Transluminal Coronary Angioplasty

Coronary Stent

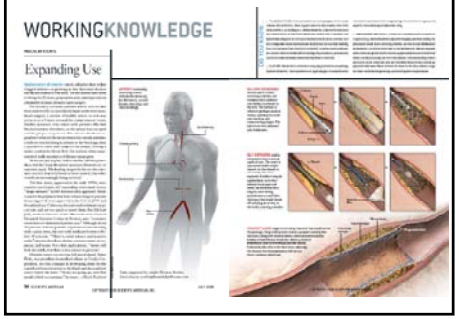
1993



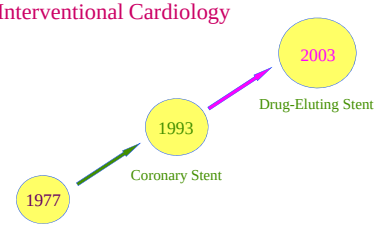


USE A TINY SIEVE TO DIVERT DEADLY BLOOD CLOTS

February 23, 2004 | BusinessWeek | 113



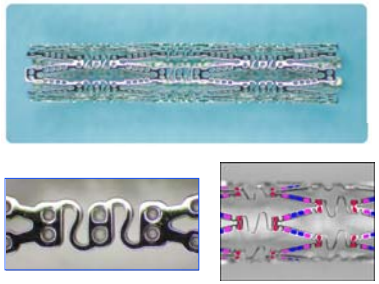
Interventional Cardiology



Balloon Angioplasty

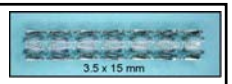
Percutaneous Transluminal Coronary Angioplasty

The Conor Drug Eluting Stent Design

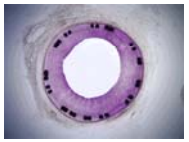


Drug-Eluting Stent

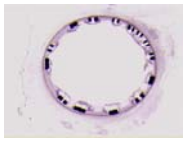
2003



Bare metal stent



Drug-eluting stent



Unparalleled Benefits

Prevention of restenosis by drug-coating on stents

Business reports on DES

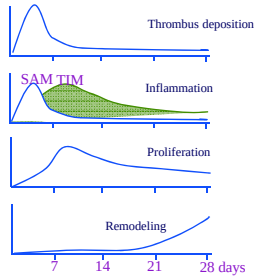
" An improved understanding of the coronary vascular response to injury after implantation of a drug-eluting stent will be required in order to develop future generations of devices that can minimize or eliminate the risk of late stent thrombosis "

- William H. Maisel, M.D., M. P. H.

" Current Status - Need has arised to investigate behind the hyperbole for DES"

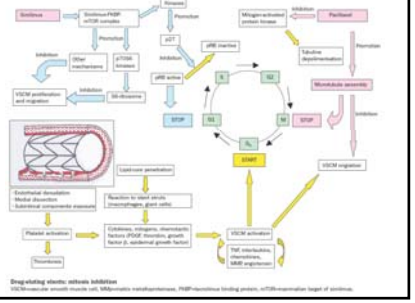
US News & World Report
December 11, 2006, p82

Time-Dependent Pathobiologic Process After Stent Replacement



modified from Edelman ER, Rogers C. Am J Cardiol. 1998

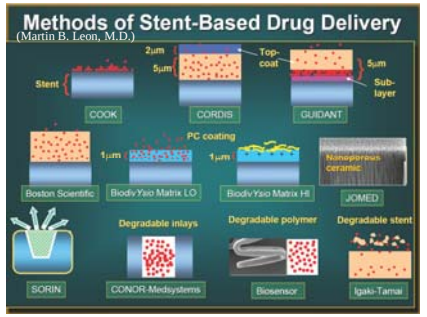
Candidate Drugs for DES



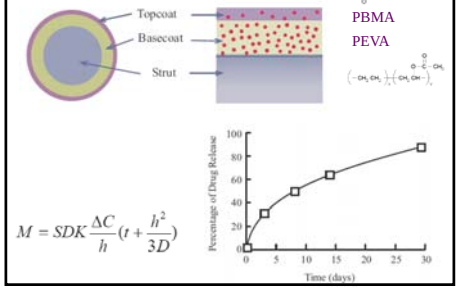
Drug-eluting stents: mitosis inhibition

Controlled Drug Delivery System	Drug-Eluting Stents (DES)
1. Drug	Paclitaxel, Sirolimus
2. Platform	Stent
3. Drug Delivery Module	
Reservoir	Drug-containing layer
Rate Controller	Polymer membrane
Delivery Portal	Polymer membrane
Energy	Drug concentration

Drug Delivery Mechanisms

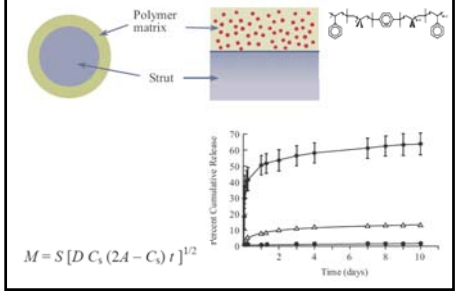


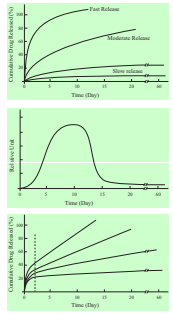
Cypher™ Stent



Taxus™ Stent

Poly(styrene-b-isobutylene-b-styrene)





Examples of release profiles of paclitaxel and sirolimus from stents. The initial release rate varies by an order of magnitude.

Proliferation kinetics of vascular smooth muscle cells after stent deployment

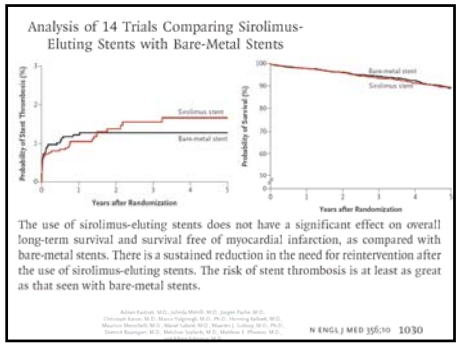
The desired drug release profiles counteracting VSMC proliferation.

Candidate Drugs for DES

Hydrophobic, Low molecular weights
Antineoplastic agents: Paclitaxel, methotrexate
Immunosuppressants: Sirolimus, tacrolimus, dexamethasone
Antihyperlipidemic: Probucol

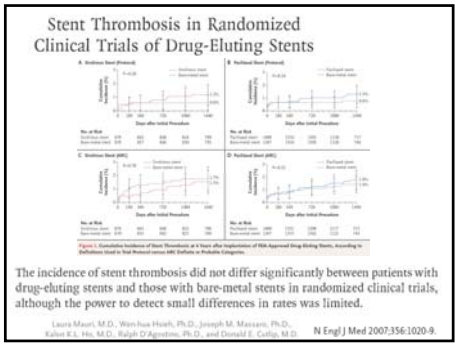
Hydrophilic, Low molecular weights
Antimetabolites: Cladribine

Hydrophilic, High molecular weights
Antisense
Ribozymes
Vascular endothelial growth factor


Analysis of 14 Trials Comparing Sirolimus-Eluting Stents with Bare-Metal Stents

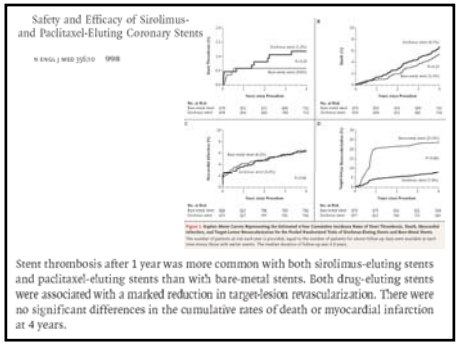
The use of sirolimus-eluting stents does not have a significant effect on overall long-term survival and survival free of myocardial infarction, as compared with bare-metal stents. There is a sustained reduction in the need for reintervention after the use of sirolimus-eluting stents. The risk of stent thrombosis is at least as great as that seen with bare-metal stents.

N ENGL J MED 356;10 1030


Stent Thrombosis in Randomized Clinical Trials of Drug-Eluting Stents

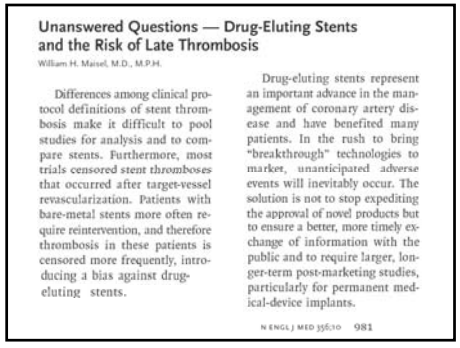
The incidence of stent thrombosis did not differ significantly between patients with drug-eluting stents and those with bare-metal stents in randomized clinical trials, although the power to detect small differences in rates was limited.

N Engl J Med 2007;356:1020-9.


Safety and Efficacy of Sirolimus- and Paclitaxel-Eluting Coronary Stents

N ENGL J MED 356;10 998

Stent thrombosis after 1 year was more common with both sirolimus-eluting stents and paclitaxel-eluting stents than with bare-metal stents. Both drug-eluting stents were associated with a marked reduction in target-lesion revascularization. There were no significant differences in the cumulative rates of death or myocardial infarction at 4 years.

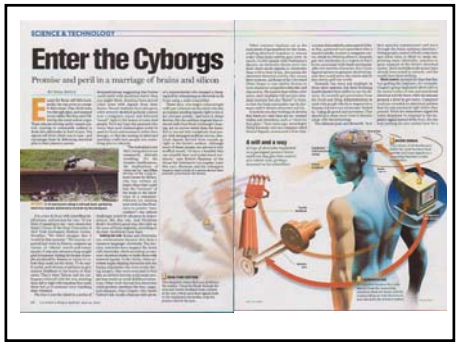

Unanswered Questions — Drug-Eluting Stents and the Risk of Late Thrombosis

William H. Maisel, M.D., M.P.H.

Differences among clinical protocol definitions of stent thrombosis make it difficult to pool studies for analysis and to compare stents. Furthermore, most trials censored stent thromboses that occurred after target-vessel revascularization. Patients with bare-metal stents more often require reintervention, and therefore thrombosis in these patients is censored more frequently, introducing a bias against drug-eluting stents.

Drug-eluting stents represent an important advance in the management of coronary artery disease and have benefited many patients. In the rush to bring "breakthrough" technologies to market, unanticipated adverse events will inevitably occur. The solution is not to stop expediting the approval of novel products but to ensure a better, more timely exchange of information with the public and to require larger, longer-term post-marketing studies, particularly for permanent medical-device implants.

N ENGL J MED 356;10 981



Biocompatibility Issues with Biomaterials

The failure of wholly synthetic materials to integrate with the biological environment.

The new generation biomaterials

Newer biomaterials development to incorporate the basic structural elements of human tissues, such as proteins, glycosaminoglycans (GAGs), minerals, and even cells.

Biomaterials with more interaction with the cells and surrounding tissues.

One of the goals of a medical device for tissue replacement

The ability of the device to interact with the patient's own cells and the potential to allow cells to rebuild and regenerate tissue.