Cardiovascular disease ranks as the number one cause of death in the United States. It is expected to increase proportionally with the increase in diabetes, which is already showing a steady rise in this country. Because diabetes produces a significant negative impact on the vascular system, therapies to correct damage already incurred in the vessels are mounting in numbers, both here in the U.S and internationally. The United Kingdom, UK, has been exceptionally active in medical research because of the high rate of coronary artery disease (CAD), and the increase in diabetes. Research is being conducted across the globe to correct and rectify compromised coronary arteries, since CAD is impacting all populations, regardless of race, sex or ethnic background. Data regarding genetic predisposition for CAD is expected to be correlated with the information coming for Iceland’s genome project.

According to the American Heart Associations, in 2004, over 1 million angioplasties were done in the U.S, 850,000 in men and 400,000 in women, and of these, almost 700,000 were percutaneous transluminal coronary angioplasties (PTCAs). It is expected that by year’s end, over 1.2 million Americans will experience their first or repeat heart attack or myocardial infarction (MI). Ideally, it would be the goal of modern medicine and individual patients to prevent the coronary damage before it occurs, and thus reduce the requirement for post injury intervention; i.e., prevent the train wreck before it occurs. However a solid, workable, system-wide approach to the biological processes associated with heart disease needs effective planning, a realistic time table and buy in, not only by the medical, scientific, and governmental communities, but by the individual citizen. In the interim, interventional therapy must be implemented that is safe, effective, scientifically sound, cost accessible and sustainable without long-term contraindications and has a positive impact on human longevity.
Coronary arteries which surround the myocardium, supply the muscle cells of the heart with the nutrients and oxygen required for contraction. If deposits accumulate, such as cholesterol or calcium, plaque forms inside the artery wall, creating an uneven surface in the endothelium, which provides a site for additional accumulation of materials and cellular growth and matrix material which eventually decreases the diameter of the vessel or occludes the lumen, i.e., stenosis of the vessel. Decreased vessel diameter restricts blood flow significantly, reducing the supply of nutrients and oxygen to the myocardium. Coronary heart disease is caused by a narrowing or stenosis on the coronary vessels due to these fatty build-ups of plaque. This condition is termed, arteriosclerosis. Past interventions included drug therapy for vasodilation and balloon angioplasty. As early as 1977, balloon angioplasty was introduced, which merely impacted the plaque material against the artery wall for immediate pain relieve and increased blood flow. The rate of recurring restenosis in the treated vessel made the intervention short term and required repeat invasive angioplasty.

Stent implantation to widen the damaged occluded artery was the next step forward. As early as 1969, CT Dotter experimented with and implanted a coilspring graft into a canine artery. By 1987 Sigwart introduced the idea of implantable coronary stents for relief of occluded coronary vessels. In 1991, Mullins and O’Laughlin proposed intravascular balloon expandable graphs. Since then, there has been an explosion of experimental data, stent design, modifications, drug eluding implants and now, biodegradeable stents. It is estimated that stent manufacture and implementation constitutes a commodity in excess of 6 billion dollars. Obviously there is intense activity surrounding both research and manufacturing dollars.

Stents and drug therapy appear to be the current answers for inactivating thrombus formation and retrofitting and remodeling damaged artery walls, but there are some counterindications and some drawbacks to the current models. There are four currently recognized mechanisms which impact the safety, longevity, and patency (being open or unblocked) of implantable stents. These include:
• Elastic recoil – vasoconstriction due to endothelial disruption
• Mural thrombus (Fig 1)
• Neointimal hyperplasia (Fig 2)
• Vessel wall remodeling (Fig 3)

Elastic recoil or vasoconstriction caused by the invasion of the endothelium, can be counteracted by either a balloon or a mechanical stent. Recoil occurs within 24 hours post PTCA. Thrombus formation occurs within 2-3 weeks and involves activation of platelets, thrombin initiation, smooth muscle cell proliferation and migration and leukocyte movement toward the site of PCTA. Neointimal hyperplasia is the proliferation, in a blood vessel, of a new layer of endothelial cells on the intimal surface. Neoinitimal formation is commonly referred to as vascular scar tissue. Neoinitimal formation is due to smooth muscle cell (SMC) proliferation and direction migration and the appearance of monocyte/macrophage invasion at the site. This has been demonstrated using knock-out genes and antibodies against vascular cell adhesion molecules. This can be seen occurring as early as 48 hrs post PTCA and continuing over weeks to months. Vessel wall remodeling refers to a change in the artery wall size. When referring to the increase of the wall size in restenosis, this is referred to as “negative remodeling”, and results in a narrowing of the arterial lumen. Remodeling can occur independently of the other 3 factors, recoil, thrombus or neoinitimal formation. Remodeling time will vary with the individual patient’s biological immune system and tissue generation rate, which includes variables such as age, nutrition and overall system health. There is agreement within the medical and scientific community that both elastic recoil and thrombus formation are absolute factors in restenosis. There is conjecture, based on recent long term studies post PTCA, that neointimal formation and remodeling override and predominate as the causative agents in restenosis.
Fig 1. Thrombus (clot) in artery

Fig 2. Arteriosclerosis – thickening of artery wall

Fig 3. Normal artery wall
What is a stent and how is it used? A stent is a wire metal mesh tube which is used to dilate an occluded vessel during angioplasty. It is collapsed to a small diameter and pulled over a balloon catheter. It inserted intravenously through the femoral artery. Using fluoroscopy, the stent is positioned into the arterial segment, which has been predetermined by quantitative angiography. Following placement and removal of the catheter with deflatable balloon, the implanted stent was then viewed with angiography for patency and position.

Because of the very nature of an exogenous implant, stents lead to greater vessel injury, inflammation, wound healing and foreign body interaction with immunologic response.

What are the requirements for a stent? Numerous materials have been tested and used for stenting materials and some have adequate histories and others are still in the proving period. Long term pressure on the arterial walls by stents has proved disadvantageous and has led neointimal tissue proliferation in various locations, including locally, along the entire length of the stent and at the ends of the stent. It appears that this intimal proliferation is the leading antagonist of in-stent restenosis (ISR) and According to the physiological needs, stents requirements include:

- Durability adequate for healing
- Ductility
- Ability to maintain vessel patency
- Reduce (ISR)
- Reduce thrombogenicity
• Reduce or eliminate intimal proliferation
• Produce minimal toxicity
• Compatible with MRI, CT and UV/US procedures
• Biocompability
• Biodegradeable
• Cost accessible in manufacturing
• Reduce or eliminate need for long term anti-thrombotic drug therapy
• Positive remodeling
• Compatible for pediatric implant and vascular growth

An assortment of transition metals and their alloys have been tested and implanted, along with some select polymers. Initially, looking at implants used in orthopedics, stents were made of a stainless steel framework. It was found, however, that the steel is not fully biocompatible and has produced a high incidence of ISR, thrombosis, bleeding complications, and corrosion. Additionally, the steel presents radiopacity which interferes with follow up radiographic images. The materials that have since been considered include gold, titanium, tantalum, cobalt-chromium alloys, cobalt-chromium-nickel-molybdenum-iron alloy, nickel-titanium alloy, and pure iron. Gold has a good history of biocompatibility and is usually inert, but is quite expensive. Tantalum is radio-opaque making it good for viewing, it is more brittle than stainless steel and is resistant to corrosion. It has been demonstrated that chromium-cobalt-nickel ions, released as extracts from corrosion of the stents have a cytotoxic effect on mononuclear cells and high concentration of these metallic ions can produce cell necrosis.

The nickel-titanium stent, “Nitinol”, is 55% nickel and 45% titanium, has a rubber-like behavior, making it elastic and easily conformable. Nitinol has a strong intermetallic bond between the nickel and titanium, thus yielding a very low reactivity rate, which is particularly important in patients with nickel sensitivity. Additionally, with low reactivity, there is less immunologic response. Nitinol is difficult to manufacture and very small changes in its composition can drastically affect its transformation.
temperature. Additionally, the titanium in the alloy is highly reactive, so alloy synthesis must be carried out in a vacuum. Difficulty in manufacturing translates to increased dollars for production of the stents. Many of the metallic stents have retrofitted as drug eluding stents (DES) to reduce thrombus and intimal formation.

Polymers for stents include polyethylene or polyurethane. Silicone was the first organic material used for polymer stenting. Silicone has poor biodurability, tensile and coil strength, which would exacerbate recoiling and restenosis. Polyethylene produces protein adherence and biofilm formation in vivo and is a reactive material, which increases immunological responses. Additionally, there has been evidence that in the degradation of polymers, some of the particles or remnants can circulate and act as thrombus initiators elsewhere in the cardiovascular system. Some biodegradable polymers, like polyesters and polyanhydrides, have been used as drug delivery devices, which will degrade via normal hydrolytic biological processes.

Obviously, biocompatibility is a key factor in consideration of the material for an implantable coronary stent. Of all the transition metals which have been investigated, iron appears to be the most biocompatible because of its overall presence throughout the biological system. Peuster, et al, from Children’s Hospital, Goettingen, Germany, were the first to examine the use of degradable metallic stents in coronary stenting. They developed a corrodeable iron stent, (NOR-1) that was produced from pure iron (>99.8% iron) and laser cut to a slotted tube design. These biodegradable stents were implanted into New Zealand white rabbits and followed for 6-18 months. Peuster and his group were able to demonstrate that the iron biodegradeable stents produced no thromboembolic complications, no significant neointimal proliferation, no significant inflammatory response, maintenance of vessel patency, compatibility with radiographic procedures, and no systemic toxicity. The amount of pure iron implanted in the stent amounted to 41 mg which equals the monthly oral intake of iron. A unit of transfused blood contributes approximately 200-250 mg of iron.
According to Peuster’s group, the rate of degradation of iron in the system is not yet assessed, but it is understood that the stent must be in place for at least six months in order to ensure tissue healing and no fragment embolisation of the vessel. They will investigate the possibility of an iron alloy, including an iron-carbon alloy, or modification of the surface and structure to promote faster degradation.

Mueller, et al, from the Clinic for Congenital Heart Defects in Oeynhausen, Germany, conducted a study on biodegradable iron stents and the impact of these implanted devices on vascular smooth muscle cell (SMC) proliferation rate. They demonstrated that iron (II) as a degradation product of pure iron stents may play a beneficial role in reducing restenosis, by the down regulation of cell proliferation.

A novel new approach is being investigated at Mayo Clinic for targeting the direction and localization of endothelial cells to the site of coronary stenting. Pislaru, et al, have magnetized blood-derived endothelial cells which, by local delivery, will localize on a magnetized stent. They used cultured porcine cells labeled with superparamagnetic iron oxide microspheres (SPM -63.4% iron oxide; 0.9 micrometers in diameter) in a 500:1 ratio (microspheres:cells). The cells were grown in culture for 2 weeks and then
coincubated with the SPMs at 37°C for 16 hours. They investigated a variety of metallic stents, including stainless steel, chromium-cobalt-nickel alloy and Nitinol and exposed these stents to 5,000G magnetic field. These stents did not maintain any significant magnetic charge, sufficient to attract the SPM loaded cells. Magnetized nickel gave good cell attraction, but as discussed earlier, does not have good stent properties. A combination stainless steel stent, coated with a 10 mm layer of nickel was used to capitalize on the steel stent properties and the nickel magnetism. They also tested iron-loaded cells and tested them with magnetized stents under various flow rates, to mimic stress flow from cardiac circulation. The group demonstrated: a) an appropriate concentration of SPMs to cells that was not toxic; b) the magnetized cells when lodged on the surface of the stent resisted dislodgement when subject to the shear forces of circulating blood; c) the SPM labeled cells were able to form biochemical bonds at the implant site; d) the SPM labeled cells lined up along the stent struts but also spread to denuded area, increasing endothelial repair.

Areas that need to be further investigated with the Mayo research include: elimination of the magnetic charges after cells have bonded biochemically; displacement of nickel with other substitutes because of allergic responses to the metal; further quantitation of exposure to iron oxide over various time intervals. Implications of delivery magnetized cells to specific locations within the biological system, can trigger new avenues for therapeutic and drug delivery systems.
References:


