Biocompatibility Aspects of New Stent Technology

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Stent implantation represents a major step forward since the introduction of coronary angioplasty. As indications continue to expand, better understanding of the early and late biocompatibility issues appears critical. Persisting challenges to the use of intracoronary stents include the prevention of early thrombus formation and late neointima development. Different metals and designs have been evaluated in animal models and subsequently in patients. Polymer coatings have been proposed to improve the biocompatibility of metallic stents or to serve as matrix for drug delivery and they are currently undergoing clinical studies. The introduction of coronary angioplasty. As indications continue to expand, better understanding of the early and late biocompatibility issues appears critical. Persisting challenges to the use of intracoronary stents include the prevention of early thrombus formation and late neointima development. Different metals and designs have been evaluated in animal models and subsequently in patients. Polymer coatings have been proposed to improve the biocompatibility of metallic stents or to serve as matrix for drug delivery and they are currently undergoing clinical studies. The promise of a biodegradable stent have not yet been fulfilled although encouraging results have recently been reported. Continuous low dose-rate brachytherapy combining the scaffolding effect of the stent with localized radiation therapy has witnessed the development and early clinical testing of radioactive stents. The combined efforts of basic scientists and clinicians will undoubtedly contribute to the improvement of stent biocompatibility in the future.

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advantages that have not yet been fully explored in the clinical setting (9). Nitinol alloy has also proved to have good early biocompatibility. Some concern exists that nickel leakage from these alloys could lead to immunogenic reactions (8,10,11). Tantalum confers several theoretical advantages over stainless steel in terms of radiopacity, biocompatibility, mechanical properties and lack of ferromagnetism. It is regarded as a biologically inert material. After implantation, the tantalum stent wire undergoes oxidation, resulting in an oxide that is very stable and extremely resistant to degradation (3). In the circulation, the thin layer of inert tantalum peroxide creates an electrically negative charge that could reduce adhesion of negatively charged platelets (12). However, in clinical practice, tantalum has not been shown to decrease stent thrombosis compared with stainless steel stents. This may be partly due to the activation of the coagulation cascade by negatively charged surfaces (13). Therefore, whether the metallurgical properties may confer an advantage in vivo is still unknown. Scott et al. (14) found no difference in platelet deposition and fibrin accumulation between identical coil stents made of tantalum or stainless steel in baboon arteriovenous shunts and in porcine coronary arteries. Rogers and Edelman (15) compared vascular injury, thrombosis rates and neointima formation between stainless steel slotted tube (Palmaz-Schatz) and stainless steel corrugated ring stents (Multilink) in rabbit iliac arteries. These two stents have distinct designs but identical metals and metal-to-surface ratios. Overall neointima formation was proportional to vessel injury and corrugated ring stents created 42% less arterial injury and 38% less neointimal hyperplasia than slotted tube stents. Polymer coating (Thromboshield) had no effect on vessel injury or neointima formation but significantly decreased thrombosis rates. Altering the stent surface with a polymer coating virtually eliminated thrombotic occlusion in corrugated ring stents and significantly reduced thrombosis rates in coated versus uncoated slotted-tube stents (8% vs. 42%, respectively). Barth et al. (16) performed paired comparisons of vascular wall reactions after implantation of 3 different stents in dog peripheral arteries. Neointima formation was significantly higher with Streeker stents than with Wallstent or Palmaz stents. Sheth et al. (17) described less thrombosis and vessel injury after implantation of slotted tube nitinol stents in rabbit carotid arteries compared with Palmaz-Schatz stents. In an attempt to separate the multiple factors involved in stent performance, Fontaine et al. (18) compared similarly designed tantalum coil stents with different rigidity. The more rigid stents induced more vessel injury and created more neointima than the flexible design. Buchwald et al. (19) compared regular and short-wave Wiktor stents implanted in minipig coronary arteries. Although neointimal area was reduced at 4 weeks in the short-wave group, no difference subsisted in neointimal or lumen area between the 2 groups at 12 weeks. Therefore, the increased metal mass (15%) associated with the short-wave design did not lead to increased neointima formation. Many factors such as blood rheology, longitudinal flexibility, metal hoop-strength and coverage may interfere with and complicate the objective evaluation of stents with different designs.

Furthermore, surface treatment has also been shown to modify the performance of stents. Sheth et al. (20) compared the effects of mechanical polishing to decrease surface irregularities on thrombosis in an ex vivo porcine arteriovenous shunt model. Polished nitinol slotted-tube and Palmaz-Schatz stents exhibited a drastic reduction in thrombus formation compared with unpolished nitinol stents. De Scheerder et al. (21), using electrochemical polishing of stainless steel stents, showed a significant reduction in early thrombosis in a rat arteriovenous shunt model and less neointima formation in a pig coronary model compared with untreated stents. Other investigators have also tested noble metal coatings to improve the corrosion properties (22,23). However, no distinct advantages in terms of thrombus or neointima formation were found between metal coatings by galvanization or ion implantation compared with uncoated stents. Thus, experimental data suggest that stent design and surface properties may influence early and late results of stenting in animal models. Ongoing randomized trials comparing various stent designs will soon confirm whether this translates into different clinical outcomes.

**Polymer coatings (Table 1).** Polymers are long-chain molecules that consist of small repeating units (8). Several polymers with previous medical or dental use have been evaluated to cover stents or to coat stent struts.

**Nonbiodegradable synthetic polymers.** Van der Giessen et al. (24) compared thrombosis rates and neointima formation using uncoated and coated Wallstents with Biogold (Plasma Carb Inc.). Despite suppression of early thrombosis with the coating, neointima formation remained similar in both groups after 12 weeks. A large group of investigators have evaluated 3 synthetic nonbiodegradable coatings partially covering coil tantalum stents (25). Three different nonsterile polymers were implanted in a pig coronary model: polyurethane, poly (di(methyl) siloxane (silicone) and polyethylene terephthalate (Dacron). All but one of the 20 silicone-coated stents remained patent at 4 weeks. All polymers elicited intense inflammatory responses with presence of multinucleated giant cells and macrophages surrounding proteinaceous debris and thrombus remnants. De Scheerder et al. (26) compared 2 different polymer coatings of stainless steel slotted tube stents in normal porcine coronary arteries. Stents were coated with either a biodegradable poly(organophosphazene) (POP) or a biostable polyurethane. Although 3 of 6 pigs with uncoated stents died of acute stent occlusion, only one of four POP-coated stents was found occluded at follow-up angiography. No difference in neointima proliferation was found between bare and polyure-
thane stents. However, in the POP-coated stent group, severe intimal proliferation of histiolympocytic tissue was noted. Fontaine et al. (27) compared platelet adhesion between uncoated and polyurethane-coated tantalum stents implanted in a swine arteriovenous shunt. Radiolabeled platelet accumulation in the uncoated stent group was already more severe after 5 min and remained higher after 60 to 120 min. In rabbit carotid arteries, Rechavia et al. (28) observed identical tissue reaction between polyurethane-coated and uncoated nitinol stents. Chronos et al. (29) used a copolymer of methacrylphosphorylcholine and laurylmethacrylate to coat stainless steel stents. In a baboon arteriovenous shunt model, they observed an early decrease in platelet deposition at 60 and 120 min compared with bare stents. Subsequently, Malik et al. (30) evaluated phosphorylcholine (a component of cell membrane) or cross-linked phosphorylcholine coated on stainless steel stents in a pig coronary model. No stent thrombosis occurred in any group and there was no excess neointima formation in coated versus uncoated stents. Identical results have been obtained in rabbit iliac arteries with phosphotidylcholine by Nordrehaug and colleagues (31). Amon et al. (32) used a newly designed tantalum stent with a silicon carbide coating. In vivo testing in a pig model showed the absence of thrombus formation. Ozbek et al. (33), using the same coating applied on stainless steel stents reported the first clinical use in bail-out stenting. Among 44 patients who received 58 silicon-carbide coated stents, 21% (9 of 42) had restenosis at 6-month follow-up and stent thrombosis was suspected in two patients. Thus, these results do not seem to suggest a clinical advantage for these silicone-carbide coated stents. Therefore, it remains unclear whether any polymer coating may improve the stent biocompatibility per se, but recent data suggest that some polymers such as polyurethane or phosphorylcholine could serve as effective drug delivery systems.

### Biodegradable synthetic polymers

Van der Giessen et al. (25) studied 5 polymer-coated stents implanted in pig coronary arteries. Polyglycolic/polyactic acid copolymer, polyacrylactone, polyhydroxy-buturate/valerate copolymer (PHBV), poly-
Table 2. Heparin-Coated Stents

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Model</th>
<th>Stent</th>
<th>Coating</th>
<th>Control</th>
<th>Thrombosis Reduction</th>
<th>Neointima Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonan et al. (41)</td>
<td>Dog coronary</td>
<td>Zig-Zag</td>
<td>NA</td>
<td>Bare stent</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Stradienko et al. (42)</td>
<td>Rabbit iliac</td>
<td>Palmaz-Schatz</td>
<td>—</td>
<td>Bare stent</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Bailey et al. (43)</td>
<td>Rabbit iliac</td>
<td>Palmaz-Schatz</td>
<td>Proprietary</td>
<td>Bare stent</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sheth et al. (44)</td>
<td>Rabbit carotid</td>
<td>Harts</td>
<td>SPUU-PEO-hep</td>
<td>Bare stent</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Hardhammar et al. (45)</td>
<td>Pig coronary</td>
<td>Palmaz-Schatz</td>
<td>Carmeda</td>
<td>Bare stent</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Serruys et al. (46)</td>
<td>Human coronary art.</td>
<td>Palmaz-Schatz</td>
<td>Carmeda</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Chronos et al. (47)</td>
<td>Baboon carotid</td>
<td>Cordis</td>
<td>NA</td>
<td>Bare stent</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronos et al. (48,49)</td>
<td>Baboon A-V</td>
<td>Palmaz-Schatz</td>
<td>Carmeda</td>
<td>Bare stent</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Zidar et al. (50,51)</td>
<td>Dog coronary</td>
<td>Cordis</td>
<td>NA</td>
<td>Bare stent</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>de Scheerder et al. (52)</td>
<td>Pig coronary</td>
<td>Self designed</td>
<td>Duraflow</td>
<td>Bare stent</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Jeong et al. (54)</td>
<td>Porcine carotid</td>
<td>Wallstent</td>
<td>NA</td>
<td>Bare stent</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vrolix et al. (56)</td>
<td>Human coronary art.</td>
<td>Wiktor</td>
<td>Hepamed</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Art. = artery; A-V = arteriovenous; NA = not available; SPUU-PEO-hep = polyurethaneurea-polyethylene oxide-heparin.

orthostere and polyethyleneoxide/polybutylene terephtalate copolymer (PEO/PBTP) were used as strips covering 90 degrees of a Wiktor stent circumference. In contrast to similar studies using nonbiodegradable polymers, 3 of 7 stents with PHBV and 3 of 10 with PEO/PBTP occluded within hours after implantation. A wide range of inflammatory response was also demonstrated. Lincoff et al. (34) evaluated low (80 kD) and high (321 kD) molecular weight poly-l-lactic acid (PLLA) coated onto Wiktor stents again in pig coronary arteries. In the group with low molecular weight PLLA, severe acute and chronic signs of inflammation were recognized with a variable destruction of the vessel architecture. In contrast, in the group with high molecular weight PLLA (slower degradation), there was no evidence of acute or chronic inflammation, and the neointima was similar to that noticed in the control group. A single preliminary study reported no thrombosis and little inflammation after polyphosphate ester–coated tantalum stents were implanted in pig coronary arteries (35). Among these biodegradable polymers, PLLA remains high on the list to serve as a temporary matrix for drug release.

Natural coated and covered stents. Natural products offer the theoretical advantage of minimizing the inflammatory response. Holmes et al. (36) compared fibrin-covered with polyurethane-covered tantalum stents in a pig coronary artery model. Polymerization of fibrin produced a film completely encasing the stent. In addition, fibrin-covered stents were soaked in a heparin solution for 3 hours. In the other group, stents were covered with biostable medical grade polyurethane. Three of 34 fibrin-covered stents occluded within 48 hours. After 4 weeks, all stents were endothelialized. In contrast, in the group with polyurethane covering, 6 of 12 stents occluded within 48 hours. In addition, after 4 weeks, neointimal proliferation in the group with polyurethane coating completely obliterated the lumen of the remaining stents. Histology documented an intense foreign-body reaction with multinucleated giant cells. Baker et al. (37) using a similar fibrin coating on self-expanding titanium stents and balloon-expandable Palmaz-Schatz stents, reported a significant reduction in platelet deposition after 2 hours in an in vitro model. Subsequently implanted in canine iliac arteries, 3 of 7 uncoated stents thrombosed after 8 weeks, whereas no coated stent presented signs of thrombosis. In addition, foreign body reaction was observed in 2 uncoated stents but not in fibrin-coated stents. Endothelial coverage was also higher in the fibrin-coated group, suggesting that fibrin could also allow rapid endothelialization of the stent struts (38). Stefanidis et al. (39) introduced the concept of a conventional stent completely covered by an autologous vein or arterial graft. In a pig iliac artery model, they inserted 27 regular or vein-covered stents. Two uncovered stents developed subacute thrombosis. With a follow-up extending up to 6 months, covered stents showed only minimal hyperplasia (39). These results prompted the investigators to use the same technique in patients and preliminary clinical results are encouraging (40,41). Because of its relative complexity, the potential long-term benefit will be the primary factor that will determine the place of this technique.

Heparin-coated stents (Table 2). Bonan et al. (41) were first to use heparin-coated (a preliminary version of Carmeda coating) zig-zag stents in canine coronary arteries. Neither thrombosis nor neointima formation was different between coated and uncoated groups. Several preliminary reports, however, suggested that heparin coating could reduce early thrombosis (42–44). The Rotterdam group reported experimental and early clinical results with heparin-coated (Carmesa) Palmaz-Schatz stents (45,46). In their experimental series, stent thrombosis occurred in 37% of pigs receiving uncoated stents, whereas no thrombosis was seen in any coated stent with either moderate or high heparin activity. After 4 weeks, histomorphometric analysis showed a slight but significant increase in neointimal thickness in the group with highest heparin activity. However, after 12 weeks, the difference was no longer significant. Heparin coating induced a decreased endothelial cell covering of the coated stents, possibly by an effect of heparin on cell attachment and growth. The Carmesa coating also appears to be highly effective in reducing platelet deposition when stents are not completely deployed (47). Using heparin-bonded tantalum coil stents, Chronos et al. (48,49) showed similarly less early thrombosis and subsequent
Table 3. Drug-Eluting Stents

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Polymer</th>
<th>Drug</th>
<th>Amount</th>
<th>Release/Kinetics</th>
<th>Control</th>
<th>Thrombosis Reduction</th>
<th>Neointima Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lambert et al. (57)</td>
<td>PUR</td>
<td>Forskolin</td>
<td>1.58 mg</td>
<td>95% in 24 h</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dev et al. (58)</td>
<td>PUR</td>
<td>Forskolin</td>
<td>1.5 mg</td>
<td>95% in 24 h</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>de Scheerder et al. (59,60)</td>
<td>POP</td>
<td>Methylprednisolone</td>
<td>300 µg</td>
<td>86% in 24 h</td>
<td>—</td>
<td>—</td>
<td>POP stent</td>
</tr>
<tr>
<td>Cox et al. (53)</td>
<td>CEL</td>
<td>H, Metho, H+Metho</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Bare stent</td>
</tr>
<tr>
<td>Lincoff et al. (34)</td>
<td>PLLA</td>
<td>Dexamethasone</td>
<td>0.8 mg</td>
<td>&gt;50% in 2-3 d</td>
<td>PLLA</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>Eccleston et al. (61)</td>
<td>PLLA</td>
<td>Colchicine</td>
<td>3.96 mg</td>
<td>50% in 28 d</td>
<td>Bare stent</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Schmidmaier et al. (64)</td>
<td>PLLA</td>
<td>PEG-hirudin PG12</td>
<td>—</td>
<td>52.8% in 30 d</td>
<td>Bare stent</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Alt et al. (62–65)</td>
<td>PLLA</td>
<td>PEG-hirudin PG12</td>
<td>10 µg</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Aggarwal et al. (66)</td>
<td>CEL</td>
<td>Ib-Ila inhibitors</td>
<td>—</td>
<td>60% in 14 d</td>
<td>—</td>
<td>CEL ± anti-CMV</td>
<td>Yes</td>
</tr>
<tr>
<td>Aggarwal et al. (67)</td>
<td>CEL</td>
<td>Ib-Ila-UK</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>CEL</td>
<td>Yes</td>
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<tr>
<td>Folts et al. (69,70)</td>
<td>PSNO/BSA</td>
<td>NO</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Bare stent</td>
<td>Yes</td>
</tr>
<tr>
<td>Baker et al. (71)</td>
<td>FIB</td>
<td>RGD</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Bare stent</td>
<td>Yes</td>
</tr>
<tr>
<td>Santos et al. (72)</td>
<td>PLLA</td>
<td>L 703,801</td>
<td>40 w %</td>
<td>—</td>
<td>PLLA</td>
<td>No</td>
<td>—</td>
</tr>
</tbody>
</table>

Metho = methotrexate; PEG = polyethylene glycol; UK = urokinase; other abbreviations as in Table 2.

neointima formation in baboon carotid arteries. In contrast, Zidar et al. (50,51) implanted heparin-bonded tantalum coil stents in dog coronary arteries and found no difference in early thrombosis or neointima formation between coated and uncoated stents. De Scheerder et al. (52) performed a detailed experimental study to evaluate the immediate and delayed effects of heparin coating. After 30 min in a rat arteriovenous shunt model, thrombus weight, radiolabeled platelets and fibrinogen were significantly reduced in the Duraflo II coated stent group (52). However, when subsequently implanted in pig coronary arteries, there was no reduction in neointima proliferation in the group with heparin coating compared with control stents. Cox et al. (53) evaluated the potential of heparin release from a cellulose-coated coil stent to reduce neointima formation. In porcine coronary arteries, there was no significant difference at 4 weeks between coated and uncoated stents. Jeong et al. (54) evaluated heparin release from coated Wallstents in a porcine carotid model. After 1 week, all uncoated stents were occluded, whereas all coated stents remained widely patent. Therefore, in animal models, various heparin coatings have been shown to be effective in reducing thrombosis, although a beneficial effect on neointima formation remains to be established. Serruys et al. (46) reported initial clinical experience with Carmeda heparin-coated Palmaz-Schatz stents. Overall, this study showed no stent thrombosis, and restenosis rates remained low, decreasing from 15% in the group with conventional anticoagulation to 6% in patients taking a combination of ticlopidine and aspirin. In the recently completed BENESTENT II trial comparing heparin-coated stents with balloon angioplasty, 413 patients received a stent and thrombosis occurred in only 1 case (55). Vrolix et al. (56) also reported preliminary results with a heparin covalent bound (Hepamed) Wiktor stent in 100 patients. Given the better stent deployment technique and the clinical effectiveness of the ticlopidine-aspirin regimen, both of which helped to dramatically reduce stent thrombosis, the exact role of heparin coating for stents remains to be established.

Drug-eluting stents (Table 3). Much interest has been focused on loading a drug onto a stent to limit the early thrombogenicity and late neointima formation. Drugs may be released by diffusion mechanisms or during polymer breakdown. Lambert et al. (57) by using forskolin loaded into a polyurethane (Tecoflex)-coated nitinol stent, reported a decrease in thrombosis in rabbit carotid arteries. The same group compared drug release between forskolin and etedrinate (58). Levels of etedrinate in the vessel wall peaked at 24 hours and remained high up to 72 hours after placement. Levels of forskolin peaked within 2 hours of stent placement but rapidly fell during the first 24 hours. About 50% of the original etedrinate remained in the stent at 72 hours compared with about 5% of forskolin at 24 hours. Ratios of drug levels in the vessel wall to that in blood peaked at 6,000 for etedrinate and at 780 for forskolin. This study confirmed the feasibility and efficiency of the concept of a drug-eluting stent and demonstrated the variability in release kinetics according to the chemical characteristics of the selected compounds. De Scheerder et al. (59,60) showed an improved biocompatibility of POP coating by loading the polymer with methylprednisolone or angiopeptin. Cellulose ester has been used in one study as a coating for tantalum stents with heparin and/or methotrexate bound to the polymer (53). In porcine coronary arteries, there was no difference in neointima formation between drug-coated and uncoated stents. Lincoff et al. (34)
loaded dexamethasone onto a PLLA matrix that were coated on Wiktor stents. In a low molecular weight PLLA group, dexamethasone reduced the inflammatory response observed in the PLLA group, whereas there was no difference in neointima formation between polymer-coated and bare stents in the high molecular weight PLLA group. At 28 days, the tissue concentration in dexamethasone was still 3,000 higher than in the blood, confirming the possibility of slow drug release from a polymer matrix coated on a stent. Eccleston et al. (61), using the same model-eluting colchicine, also obtained similar results at 28 days. More recently, other investigators using PLLA matrix loaded with prostacyclin and PEG-hirudin coated onto stainless steel stents described less early thrombosis and neointima formation in porcine coronary arteries than in uncoated stents (62–65).

Aggarwal et al. (66,67) showed decreased early stent thrombogenicity using cellulose matrix loaded with glycoprotein IIb-IIIa inhibitors or a complex of glycoprotein IIb-IIIa urokinase. No reduction in neointima formation was subsequently demonstrated. However, recent data showed that increased loading could be achieved, and it is thus possible that higher local doses can produce a greater biological effect (68). Folts et al. (69,70) used a polynitrosated albumin nitric oxide donor coated onto Palmaz-Schatz stents that were implanted in pig coronary arteries. Preliminary results suggest an early decrease in thrombosis and less neointimal hyperplasia. Baker et al. (71), using a fibrin-covered peak stent loaded with an arginine glycine aspartic acid peptide in an atherosclerotic rabbit model described significantly less smooth muscle cell proliferation, inflammation and neointima formation in the coated group. Santos et al. (72) used a composite polymer-metal stent loaded with a nonpeptide tirofiban analog and showed a significant reduction in platelet deposition after 2 h compared with bare stents in canine coronary arteries. Although the concept of a drug delivery stent is appealing, the challenges to define the right pharmacologic agent and its release kinetics further complicate the polymer issues.

**Polymeric stents (Table 4).** The group from the Mayo Clinic first reported initial results using a Dacron tubing mesh self-expanding stent (73). Two animals killed after 24 hours confirmed the correct mechanical stent deployment within the coronary vessel. However, all animals killed 4 to 6 weeks after implantation showed a stent occluded by neointimal proliferation. In addition, there was a marked chronic foreign body inflammatory response with lymphocytes, eosinophils and giant cells. In contrast, the Rotterdam group, using a similar stent implanted in peripheral porcine arteries, described higher patency rates at 4 weeks (74). Histologic analysis displayed complete endothelial cell coverage and minimal intimal thickness. A foreign body inflammatory response was noted in the neointima of all vessels and additional inflammation was noted in the media of the occluded vessels. It is therefore possible that a contaminant was present in the nonsterilized stents used by the group at the Mayo Clinic. Investigators at Kyoto University developed a biodegradable stent in polygalactic acid. All stents were successfully implanted in 15 dogs (75). Fresh thrombus was present in some struts at 3 h. Endothelialization of the stent surface occurred between 2 and 8 weeks. However, at 1 and 2 weeks, stent degradation began to occur and foreign body reaction was recognized. Zidar and colleagues (76) at Duke University have accumulated a wide experience in the development of biodegradable stents. Using PLLA designs, their stents have shown promising in vitro mechanical properties. In vivo testing in dog femoral arteries confirmed excellent scaffolding properties. The degradation was nearly complete by 9 months with minimal inflammatory response. To assess thrombogenicity and biocompatibility, 11 polymeric stents, sterilized by polyethylene oxide, were implanted after 5 minutes of heparin soaking, in a canine femoral artery model. Only 2 stent occlusions were observed due to traumatic implantation. After 18 months, limited neointima formation was present, but there was no chronic inflammatory response. Bier et al. (77) developed bioabsorbable stents in collagen I. Preliminary in vitro data showed that most of these stents could be expanded against porcine arteries when correctly matched to vessel size. Gregory and Grunkemeier (78) evaluated an elastin-based material as a means to seal the artery. Absorption of the
material into porcine arterial wall was obtained using thermal bonding with laser energy. Gao et al. (79) developed a balloon-expandable biodegradable stent made of a copolymer of coprolactone and D,L lactide impregnated with heparin. This stent could withstand collapse pressures of 300 to 700 mm Hg at 38°C. After preheating at 51°C, stents were implanted in mini-swine carotid arteries. No thrombosis or foreign body reaction was noticed after 2 months. Recently, Landau and his group (80) developed coil and tubular stents in copolymers of poly-l-lactic acid and polycoprolactone. They served also as carriers for recombinant adenovirus vectors and were implanted in rabbit carotid arteries. Clearly, the efforts to develop a fully biodegradable stent have been slowed down by the technical complexities and by the positive long-term results of metallic stents. The concept, however, together with the possibility to deliver locally large amounts of drug for an extended period of time remains appealing.

**Endothelial cell seeding.** Another interesting approach is to provide a natural coating by using genetically engineered endothelial cells. This technique has previously been used for endovascular graft coatings. In addition, these cells may be genetically modified to generate increased local fibrinolytic activity (81,82). However, initial results were marked by limited cell retention after stent expansion and pulsatile flow exposure (82,83). To overcome some technical limitations of cells seeding, Bailey et al. (84) used local delivery of endothelial cells after stent implantation in rabbit iliac and porcine coronary arteries. After 4 h, both models displayed a large number (>75%) of attached endothelial cells onto implanted stents. By 14 days, endothelial cell coverage was >90% in both treated and untreated segments. Interestingly, it has recently been shown that local delivery of vascular endothelial growth factor165 could increase endothelial regeneration after vessel injury (85). Van belle et al. (86) showed that a single dose of vascular growth factor administered locally could enhance endothelial regeneration after stent implantation in rabbit iliac arteries. Moreover, this accelerated endothelialization was correlated with a decrease in thrombosis and intimal thickening after 28 days (86).

**Radioactive stents.** Besides the use of single doses of gamma or beta rays delivered at high dose rates by intravascular catheters, radioactive stents radioactivate some technical radiobiological advantage of delivering radiation at continuous low-dose rates (87). Using stents radioactivated by particle bombardment, Herhlein et al. (88) showed a significant reduction in neointima formation in a rabbit iliac artery model, despite the fact that extended follow-up revealed that neointima formation was only delayed in the low-activity stent groups. Later, the same group and investigators at Walter Reed Army Medical Center developed a beta-emitting stent by ion implantation of 32P (89,90). Studies in pig coronary arteries and rabbit iliac arteries confirmed earlier positive results, although they also noticed delayed reendothelialization of the stented segments and increased neointima formation with certain radioactivities (89,90). Ion implantation of noble metals has been proposed to improve the corrosion properties of metal alloys (8,23). However, to obtain the required initial radioactivity with an isotope such as 32P, would raise the quantity of phosphorus above the recommended maximum limit of 316L stainless steel (91). As a consequence, the corrosion properties of the resulting stent surface would be changed. Thus, it is possible that the surface characteristics of 32P ion-implanted or particle bombarded Palmaz-Schatz stents would be modified, leading to reduced long-term biocompatibility. Another alternative would be to use an eluting system to deliver a chosen isotope from a stent platform (92).

**Discussion**

Biocompatibility has evolved from the previous notion of inert material to a more recent concept based on the ability of a material to perform with an appropriate host response in a specific environment (93). Stent implantation adds to tissue compatibility the enormous challenge of hemocompatibility. As we have described, there are several important factors involved in the design of an optimal coronary stent. Most of the mechanical properties are related to the bulk characteristics of the metal or polymer, and those related to biocompatibility are linked to surface properties. Early biocompatibility problems with stents are associated with thrombosis, inflammation and neoimtima formation. Late problems with stents can be divided in two broad categories: mechanical failure due to material fatigue resulting from the considerable stress imposed to stents by cardiac contractions, and chemical failure where corrosion or depolymerization can release potential toxic substances such as nickel, degradation products or contaminants (8,94).

To date, long-term clinical follow-up of first-generation stents has not revealed signs of mechanical failure or toxicity, although some longer stent designs showed early fatigue when implanted in animal models and during in vitro testing (unpublished results).

Stent implantation leads to greater vessel injury than balloon dilatation and can be followed by inflammation, wound healing and sometimes foreign body reaction. Recent data suggest that the stent design itself may influence the extent of injury (15,17). Metallic stents have elicited a rather limited inflammatory response, whereas coated and polymeric stents have shown more severe responses with histiolympoctic infiltrates, macrophages and giant cells typical of foreign body reaction (25,26). Reports, however, suggest that this inflammatory response can be modulated by drug release or polymer modification. In addition, the accumulation of inflammatory cells may stimulate growth factor and cytokine release and in turn promote neoimtima formation. Drug eluting stents could therefore provide an ideal tool to limit the inflammatory reaction and possibly the neoimtima formation.

The basic tenet of blood-stent interactions is that circulating cells do not react directly with the coating or the metallic stent surface (8,13,95). Within minutes after stent implantation, soluble proteins will adhere to it and rapidly form a monolayer at the surface of the foreign material. It is therefore fundamental to understand, at the molecular level, the dy-
namic process that regulates protein adsorption. Indeed, proteins will adhere according to their plasma concentrations but also depending on their surface affinity (13,95). Therefore, there will be a competition between numerous proteins to adhere to the foreign surface. Some surfaces may preferentially absorb albumin, whereas others will tie fibrinogen. The former may promote passivation of the stent surface while the latter may lead to thrombus accumulation. Protein adhesion leads to conformational changes in the protein structure initiating cell adhesion, whereas soluble proteins do not interact with circulating cells (13,95). This field is currently under active investigation, especially since the discovery of the integrin family.

Heparin coatings have been developed to provide permanent fixation or slow release from the material surface (8). There are basically three different approaches to achieve heparin coating. First, heparin may be bound by ionic interaction (49). Then, heparin is slowly released and interacts with antithrombin III to neutralize thrombin. A second approach is to incorporate heparin by blending it with a polymer. In this case, heparin is released by leaching or biodegradation of the polymer (53). The third approach, such as that developed by Carmeda, consists of heparin immobilization using end-point attachment of heparin fragments to polyamine-dextran sulfate layers that have absorbed on the stent surface (45,46). The Medtronic (Hepamed) coating uses a similar approach where unfractionated heparin is attached to a polyamine layer. This layer has been previously covalently linked to a hydrogel deposited on the stent surface (M Verhoeven, personal communication). With the first two techniques, the release kinetics and concentration of heparin determine the clinical lifetime of the coating. With the last technology, the active site of heparin remains free and heparin functions as a catalyst to permit repetitive inactivation of thrombin by antithrombin III. It has been shown that immobilized heparin retains its ability to bind thrombin for more than 4 months (8). Other anticoagulants such as hirudin have been tested, although immobilized hirudin binds thrombin indefinitely and therefore a cycle of inactivation cannot be entertained. Other research avenues involve slow-release hirudin, immobilized fibrinolytic enzymes or new antiplatelet agents such as glycoprotein IIb-IIIa inhibitors or glycoprotein Ib antagonists. Whether early reduction in thrombogenicity will translate into reduction in neointima formation and ultimately restenosis remains, however, to be demonstrated.

**Conclusions.** Stents represent a major advance since the introduction of coronary angioplasty. As stents may be implanted in smaller vessels and in more complex lesions in the near future, the biocompatibility aspects need to be further analyzed and mastered. There is little doubt that the next decade will witness the emergence of much less thrombogenic coronary endoprostheses capable of being accepted and tolerated by the body environment. Indeed, the research in the direction of reduction in stent thrombogenicity and in providing better tissue compatibility may have a significant impact on stent effectiveness in a variety of clinical conditions and may further expand the use of stents.

**References**


