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Editorial

Stenting of coronary arteries. Are we the sorcerer's apprentice?

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Introduction

The original work of Andreas Gruentzig in 1977[1] provided the stimulus for the rapid technological growth of interventional cardiology. More recently there has been an explosion in the number of new devices designed to ablate coronary artery narrowings, recanalize occluded vessels, and prevent restenosis, so much so that it is currently difficult to evaluate the relative merits of each and to define their place in clinical practice. In many of these areas the cardiologist has been acting solely as technician, limiting his concern to the technical and procedural aspects, and sometimes overlooking the complex biological and physiological mechanisms of atherosclerosis in general, and more particularly of the restenosis process.

In achieving the perceived benefit of the therapeutic intervention with these devices the vessel wall is subjected to thermal and mechanical insults which may have hidden long-term consequences as novel as the restenosis process was when this new pathological mechanism was first described[2,3], and which has now been iatrogenically induced in tens of thousands of patients.

One of the most recent developments has been the use of the intravascular stent[4], although the original concept of intravascular stenting preceded the introduction of coronary artery interventional cardiology by many years. In 1969, Dotter developed a coilspring endovascular prosthesis in an attempt to improve the long-term patency of peripheral atherosclerotic vessels submitted to recanalization and dilatation. Even at that time he envisaged that 'prompt fibroblastic development and a rapid formation of a new, firmly anchored autogenous lining surface' would be a critical factor in the long-term patency of the device[5].

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Since the original description of Dotter's tubular coil spring[5], there have been many variants of the original concept deployed experimentally, including: thermal shaped memory alloy stents[6–8], self-expanding steel spirals[9–12], self-expandable stainless steel mesh stents[13–15], balloon expandable stainless steel mesh stents[16–19], balloon expandable interdigitating coils[20,21], synthetic polymeric stents and biodegradable stents[22]. These various devices differ greatly in their fundamental geometry (mesh, single wire), composition (metal, plastic) and mechanical behaviour (active or passive expansion). Besides these fundamental differences, there are a variety of subtle dissimilarities which may be important in themselves, such as thickness of filaments, alloy composition, electrostatic behaviour, biocompatible or therapeutic coatings[23]. The prolonged presence of these materials residing in the arterial wall may generate late unknown and unexpected consequences.

What is the rationale for stenting an atherosclerotic vessel during or after dilatation?

In the first place, the stent may optimize the dilatation process, by containing the irregular surface of the atherosclerotic plaque created by the disruptive action of the balloon. Two potential adverse effects, distal embolization of macroscopic debris originating from the plaque and a protruding obstructive flap may be contained by the stent acting as a scaffolding device. The balloon expandable stent in particular may be advantageous when the operator electively uses the device to dilate the lesion and implant the stent in a single manoeuvre. The self-expanding stent on the other hand, by exerting a continuous radial force, has the effect of increasing the diameter of the lumen until a balance is reached between the expanding force of the stent and the circumferential compliance of the vessel[4,24]. The physiopathological consequence of this is

unknown, but recently this interaction has been documented to continue for at least 24 h and possibly longer, resulting in continued improvement in the vessel lumen over and above that obtained at implantation[25]. The recoil phenomenon which is poorly documented and probably underestimated as a cause of 'restenosis' will be equally prevented by both types of stent[26]. In addition, both types of stent have a smoothing effect which reduces the turbulent and laminar resistances and may be beneficial in preventing restenosis[14,15]. Much has been made of the ability of the stent to prevent restenosis, with various theoretical proposals as to how this can be achieved and why one particular design might be more effective than another[4,20]. An attractive concept which favours the rigid stent is that the limitation of vessel wall stress seems to be protective against atherogenesis[27]. The self-expanding stent, by stretching the wall, might have the effect of accelerating the restenosis process. However, whether the accelerated process is mostly related to pulsatile stress rather than stress per se remains to be demonstrated. Although there may be some experimental work in animals to support these claims, there is as yet no evidence to support them in the clinical situation and they must therefore be regarded as speculative. There may be ultimately little difference between compliant and uncompliant devices (considering the amount of radial forces at the site of the wires exerted on the vessel wall). The initial intuitive and simplistic concept, not supported by experimental evidence, that the stent may act as a barrier preventing the migration of cellular structures (monocytes, macrophages, smooth muscle cells) into the intima during the healing process, has not been realized and the other potential mechanisms of prevention of restenosis, by stenting the internal wall of the vessel, have not yet been fully elucidated or unequivocally demonstrated. An alternative mechanism is that chronic compression by the stent of vasa vasorum underlying an atherosclerotic plaque may result in ischaemia of this microscopic vascular network and thereby limit the subsequent progression of the atherosclerotic plaque[28].

The mechanism of restenosis prevention put forward by Palmaz *et al.*[18] is open to criticism on the basis that it is an interpretation too dynamic for what is in essence a series of post mortem 'snap shots' which are difficult to reconstruct in time (Fig. 1). This evidence, recently reiterated by Schatz, is extremely appealing and attractive, but remains an unsubstantiated interpretation[29]. The struts of the mesh prevent the protrusion of sizeable atherosclerotic plaques inside the lumen of the vessel and act as a 'macroscopic sieve', containing and pushing the atherosclerotic plaque away from the neo-intimal lining into the adventitia. In addition, a sclerotic thinning of the media is apparently induced, converting the muscular and dynamic medial layers of the vessel into a practically non-vasoactive and non-compliant 'pipe'. Whether this is true and applicable to the human clinical situation remains to be demonstrated.

There is a consensus among investigators in the field that stent implantation improves the immediate post-dilatation result, producing a smooth straight appearance of the dilated segment. This visual impression has been confirmed by quantitative analysis using both edge detection and video densitometric techniques[24]. Favourable results have also been reported in the 'bail-out' situation, when the stent has been implanted following dilatation where presence of intimal dissection had led to a poor and even critical haemodynamic result[30,31].

The thrombogenic nature of the stent remains a concern, although there may be important differences between different devices[29,32,33]. This concern is reflected in the anticoagulant regimens used in patients in whom the Medinvent stent was implanted (Table 1). This complex and aggressive protocol reflects the insecurity of the clinician and the knowledge that none of the anticoagulant agents on their own will reliably prevent thrombus formation. It is a paradox that similar devices, although with different metallic compositions, have been used for just the opposite effect — to create thrombotic occlusion in experimental animals[34–36].

At the tenth congress of the European Society of Cardiology, Richard Schatz reported the immediate results in 15 patients who had received a Palmaz stent. According to an FDA-approved protocol, the stents were implanted in vessels (mostly right coronary arteries) supplied by a collateral circulation. At that time he was convinced that all patients could be treated with heparin and dextran during the procedure and aspirin and dipyridamole alone after discharge. There were no instances of abrupt closure and no patient required warfarin. These initial results suggested that this balloon expandable stent was relatively non-thrombogenic, which eliminated the need for both routine administration of lytic agents during the procedure and warfarin thereafter. Unfortunately, the angiographic follow-up at 6 months of these first 15 patients

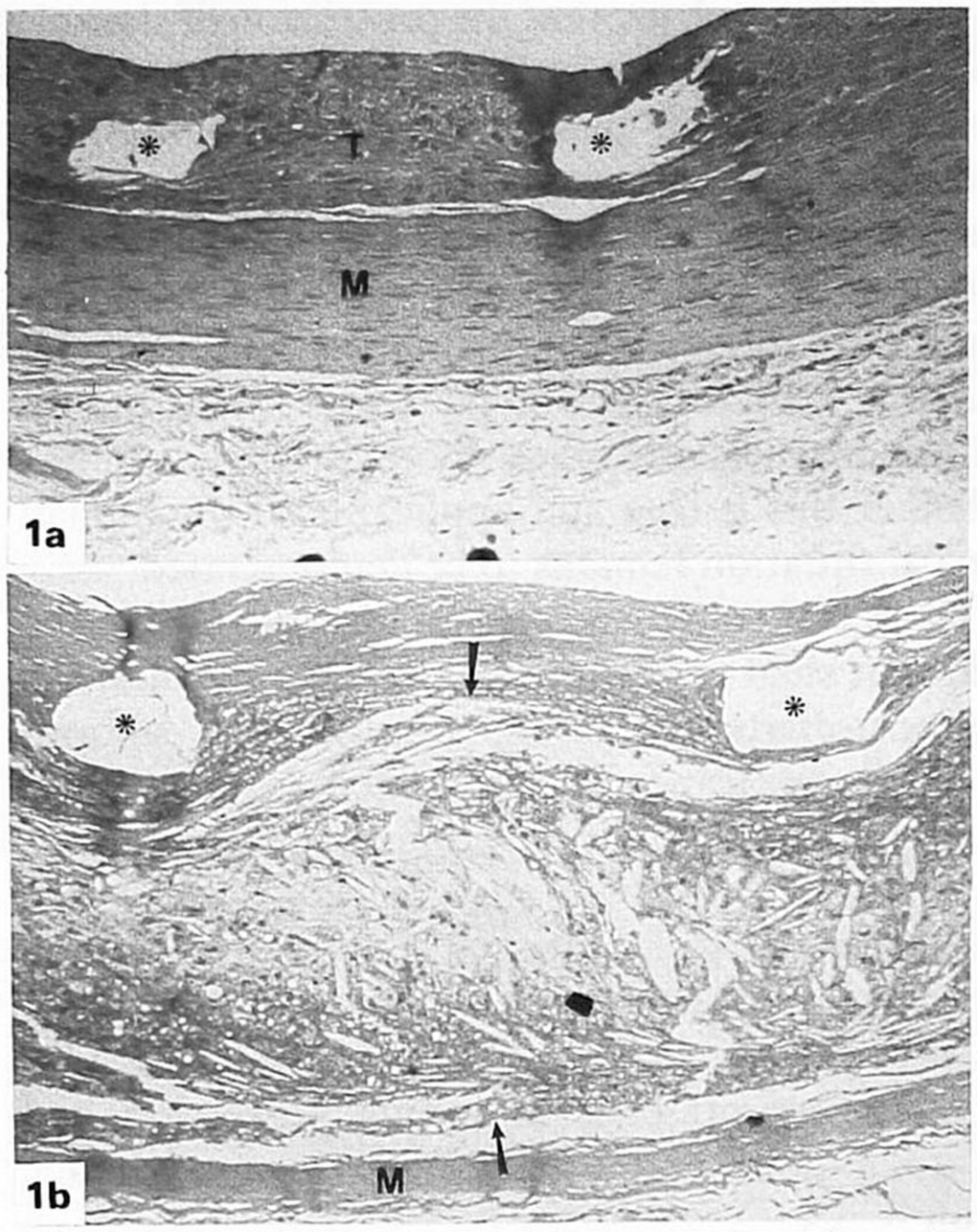

Figure 1 Microphotography of cross section of an atherosclerotic rabbit aorta (a) 1 week and (b) 6 months after stenting. Note the thin layer of thrombus (T) covering the stent struts (*) and the thick media (M) at 1 week. By 6 months, thrombus is replaced with acellular ground substance and endothelium. A large plaque is evident (arrows) but does not encroach the lumen (from Schatz[29], reprinted with the permission of *Circulation*).

disclosed four total occlusions and one restenosis. Since then, patients have been given coumadin.

Concern has also been expressed as to whether the composition of the stent is able to trigger an allergic response, particularly in individuals who may be hypersensitive to the individual metals that make up the device. Although there have been reports of transient inflammatory infiltrates in the adventitia following stent implantation, it is reassuring that there are no reports of foreign body cells in the immediate vicinity of the implanted device in the experimental animal model[13,18,37]. Human data to support this assumption are still lacking, however.

Stent-induced restenosis

DO WE KNOW WHAT HAPPENS AT PTCA AND UNDERSTAND THE PROCESS OF RESTENOSIS?

Data from normal and atherosclerotic arteries of experimental animals and human autopsied hearts have shown that following balloon dilatation the arterial intima or atherosclerotic plaque may split down to the internal elastic membrane[2,3,38]. Frequently also damage of the arterial media with overdistension and splitting occurs. Next to or partially as a result of locally turbulent blood flow, a complex interaction between the exposed subendothelial surface and blood elements occurs. This results in platelet deposition locally in the region

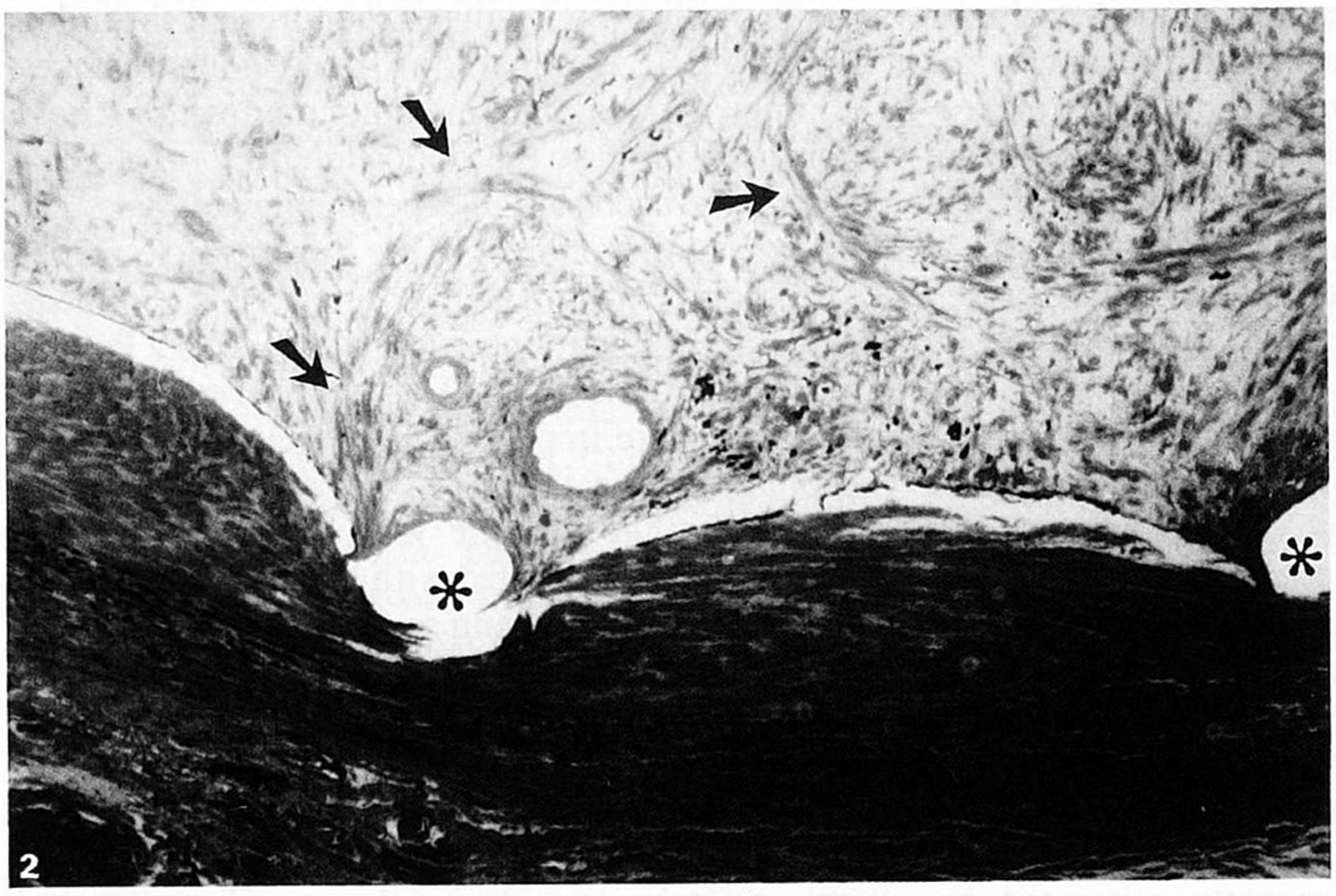

Figure 2 Histologic cross-section of a porcine left descending anterior coronary artery 1 month after stent placement (magnification × 120). The voids marked (*) originally contained the stent wires. In the neointima strands of elongated cells (arrows) are present in abundance.

Table 1 Intracoronary stent: Multicenter European Trial Drug Regimen

Day before implant procedure	— Salicylic acid 2 × 500 mg — Dipyridamole 4 × 75 mg — Sulphinpyrazone 4 × 200 mg — Ca-antagonist: nifedipine 3 × 20 mg day^{-1}
Day of implant procedure	— Salicylic acid 1 × 100 mg — Dipyridamole 4 × 75 mg (Patients above 90 kg: 3 × 150 mg) — Sulphinpyrazone 4 × 200 mg
Before PTCA	— Diltiazem 5 mg — Heparin 10 000 I.U. — Dextran 500 mg. $(4\ h)^{-1}$
At implantation	— 100 000 I.U. Urokinase in 250 ml NaCl given intracoronary (i.c.) up to the end of the procedure. Start drip at guide-wire insertion given over 30–60 min and another 250 ml (100 000 I.U.) for each extra hour. — Heparin 5000 I.U. I.V.
(Post-implantation)	At start of transfer, patient to receive *heparin* at the rate of 24 000 I.U. $(24\ h)^{-1}$ to control P.T.T. at minimum 70 s. (This corresponds to about 400 I.U. kg^{-1}. $(24\ h)^{-1}$. For large patients, the maximum rate is 30 000 I.U. $(24\ h)^{-1}$. If P.T.T. > 200 s (5 × control value) the infusion is slowed. If P.T.T. < 70 s infusion flow is increased. *No less than 24 000 I.U. heparin per 24 h is to be given.*
Post-implantation (day)	Start the oral anticoagulation with acenocoumarol to be started from the first day (i.e. six tablets of 1 mg each the first day, then four the day after and two the third day and then according to 'QUICK'.
Continuing anticoagulation	— Oral anticoagulation: acenocoumarol: Quick to be maintained in the range of: 17%–25% (T.P. Thromborel S, Behring). *N.B.* Heparin will be stopped when the therapeutic level of oral anticoagulants is reached. — Salicylic acid 1 × 100 mg day^{-1} — Dipyridamole 4 × 75 mg day^{-1} (Patients > 90 kg: 3 × 150 mg day^{-1}) — Sulphinpyrazone 4 × 200 mg day^{-1} — Ca-antagonist: nifedipine 3 × 20 mg day^{-1}
Long-term	This anticoagulation regimen is stopped after the 6-month coronary angiography control. Aspirin (100 mg 1 × day) should be given ad eternam.

of the internal elastic membrane, which may be massive in the case of medial tearing, and the release of a variety of mitogens which may contribute to neointimal cell invasion and proliferation[39]. The best recognized of these factors is platelet derived growth factor (PDGF) which is released predominantly by platelets, endothelial cells as well as intimal smooth muscle cells[40]. Recently the dimeric structure of this protein has been identified[41], the three isoforms of PDGF may stimulate effects unique to each isoform through interaction with different classes of PDGF receptor[42]. There is now evidence that intimal mesenchymal cells or modified smooth muscle cells (but not medial smooth muscle cells) may themselves release PDGF[40]. This may initiate the vicious circle responsible for the sustained proliferative process as it occurs in restenosis. However, neither the conditions under which this takes place nor the triggers responsible for this event are understood. In animal experiments, for example, two types of experimental arterial injury have been described: the first induced by passive trauma such as a catheter in situ or balloon denudation of the endothelial lining, and the second induced by a more disruptive stimulus, causing not only endothelial denudation, but also tearing of the media, which is the typical sequel of balloon dilatation[39,43,44]. Both are associated with the deposition of platelets on the vessel wall, with subsequent migration of smooth muscle cells from

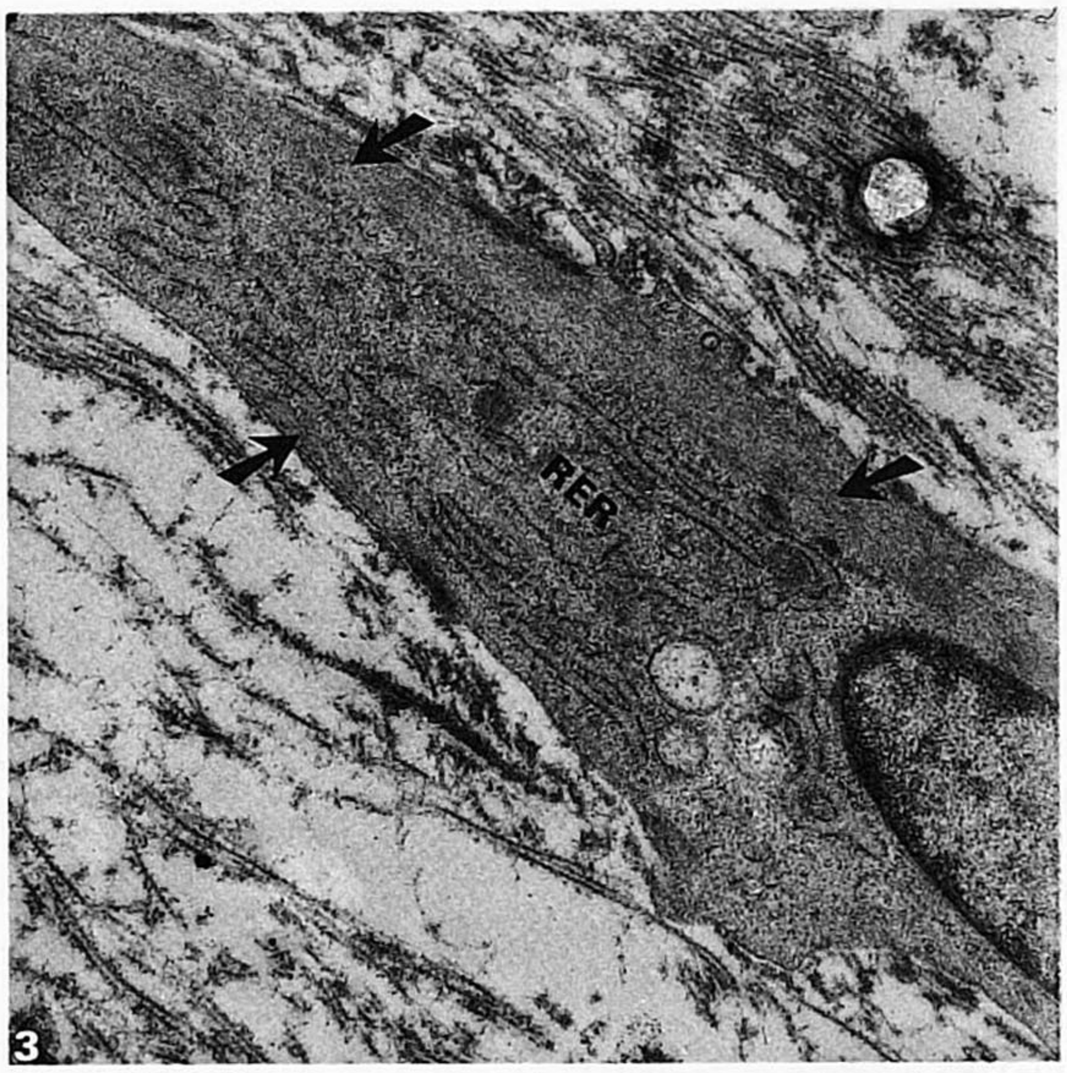

Figure 3 Transmission electron microscopy of the elongated cell-type of Fig. 2 (Magnification × 15 000). Abundant rough endoplasmic reticulum (RER) is present within these cells. Along the cell membrane bundles of myofilaments (arrows) are also prominent.

the media and their proliferation to form a neointima, and both can be prevented or inhibited by reducing the circulating platelets to very low levels. The first type, associated with repeated trauma, and presumably repeated thrombus formation, regresses following removal of the traumatizing stimulus. The second, more disruptive, type however results frequently in a lesion that is progressive in terms of smooth muscle cell proliferation and lipid accumulation. The reason that one type of lesion regresses while the other progresses is not clear. A possible explanation may come from studies on failure of synthetic arterial grafts. Once endothelial covering of synthetic grafts has progressed, smooth muscle cell proliferation appears to slow down, except in the region of anastomosis[45]. Thus a continued release of growth factors may occur even after complete endothelial covering either in areas of turbulent flow, which results in continuous endothelial damage and repair, or at sites where the barrier between neointima and media is minimal. Evidence for continued mediator release by endothelial cells under specific conditions has very recently been published[46]. The presence of a non-degradable stent in the arterial wall may form such a trigger for continued mediator release. Immediately after stent implantation its luminal surface becomes covered with a combined platelet-fibrin deposition[13]. Within 1 week of implantation into previously dilated normal porcine arteries (Fig. 2), there is complete endothelial covering of the stenting device[37] varying between 60 and 125 μm, which acts to isolate the thrombogenic stimulus from the vessel lumen. Within this layer are abundant myofibrillar cells and macrophages: the harbingers of the restenosis process. These cells can be seen to originate in the immediate vicinity of the individual stent filament adjacent to the internal elastic lamina, forming 'geysers' of elongated cells fanning out to fill the neointimal tissue in an evenly distributed fashion. In some animals this process results in complete obstruction of the stented coronary artery as early as 1 month after implantation. Electron microscopic examination (Fig. 3) of these fusiform elongated cells reveal oval nuclei with marginated chromatin, and abundant rough endoplasmatic reticulum. Bundles of contractile proteins can be demonstrated (small arrows) in a subplasmalemmal situation. These myofibroblasts or synthetic type smooth muscle cells are identical to those observed in the neointima after 1 week. It is therefore attractive to speculate that the same modified smooth muscle cells that migrate through the internal elastic membrane (IEM) and which are implicated in the restenosis process after PTCA,[46,47] can be operative in *an accelerated fashion* once a stenting device damages this natural barrier (IEM). Thus, the latter becomes more permeable to the migrating cells or providing a direct stimulus for cell migration. It has recently been suggested that restenosis following primary balloon angioplasty is an unfavourable lesion for interventions such as atherectomy and stenting[48–50]. From preliminary data presented by Simpson *et al.* at the 38th session of the American College of Cardiology, it appears that restenosis rate following atherectomy as a primary intervention is 23·5%, while the restenosis rates are 36·8%, 42·1% and 53·8% when atherectomy was performed as the secondary treatment following a first, second and third recurrence of stenosis[51]. A similar opinion has been expressed by the group of Sigwart *et al.*[48] Their preliminary data suggest that elective stenting for restenosis early after previous angioplasty carries an increased risk (41%) of restenosis within the stent. It could be that the active fibrocellular proliferation associated with the early phase of restenosis after balloon angioplasty is further stimulated by stent implantation.

In this respect, one of the questions posed by Spencer King III in his editorial is judicious and pertinent: is the treatment worse than the

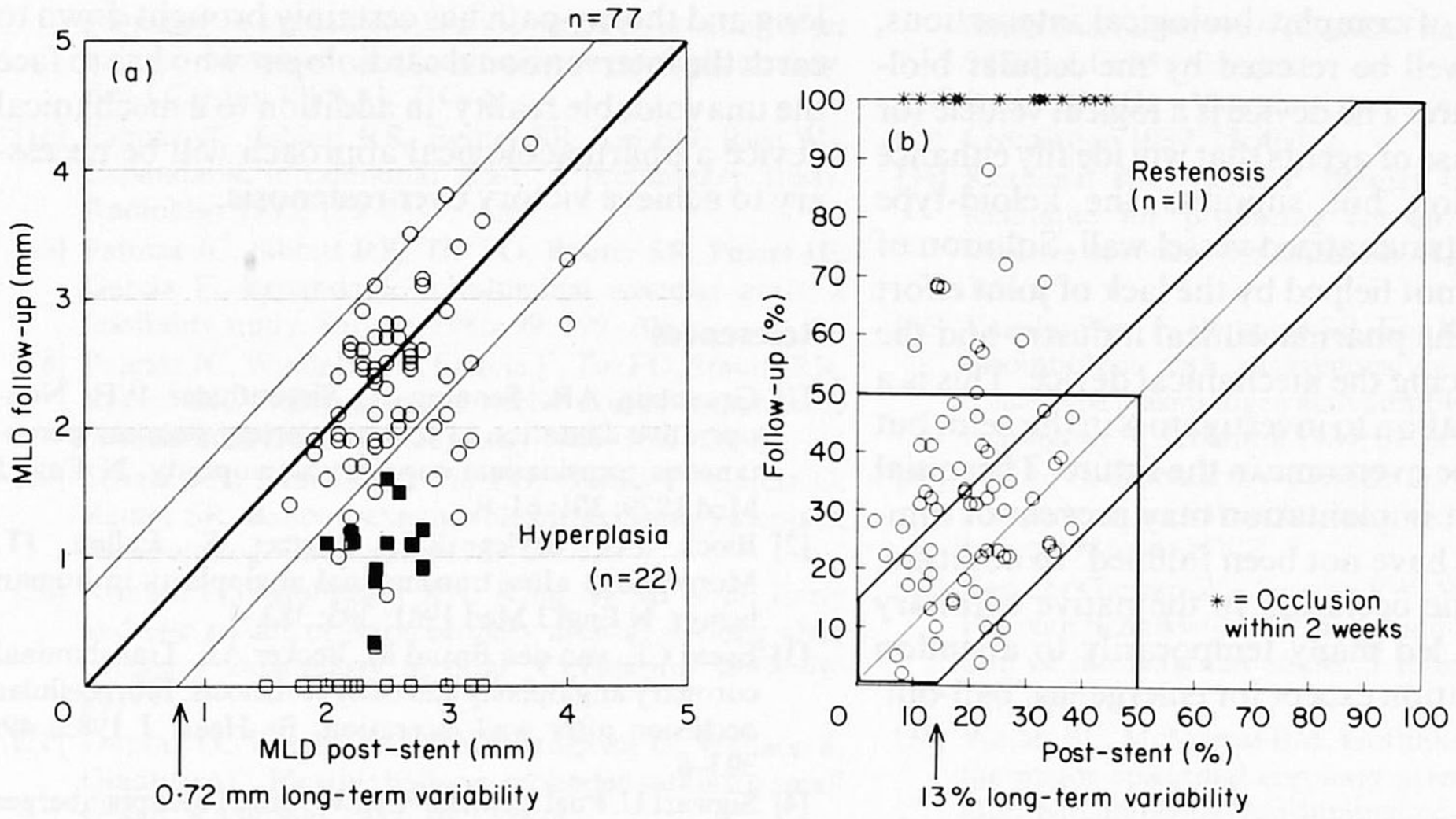

Figure 4 (a) Diagram demonstrating the change in the minimal luminal diameter following stent implantation. The individual minimal lumen diameter (MLD) immediately following stent implantation (horizontal axis) are compared with that at angiographic follow-up (vertical axis). The two lines to either side of the identity line represent the long-term variability for repeat measurement. All points (n = 22) that fall below the lower line are therefore considered to have undergone a significant deterioration (intimal hyperplasia $>0{\cdot}72$ mm) and in addition the closed blocks also fulfil the criterion of $\geq 50\%$ diameter stenosis. The open blocks represent early total occlusions (n = 13). (b) Similar diagram demonstrating the change in terms of percentage diameter stenosis. The circles falling both outside the limits of the long-term variability of quantitative angiographic measurement and have $>50\%$ diameter stenosis, represent true 'restenosis' unequivocal within the stent.

disease?[33] Perhaps a more appropriate question is whether we have to apply these more costly interventions, as the initial procedure, in order to achieve a reduction of the restenosis rate? Such is the dilemma we have to face. Certain authors have already drawn the conclusion that atherectomy, for example is a *favourable* primary approach for the treatment of selected *unfavourable* lesions[50].

The intracoronary stent like many other novel forms of treatment seems to be following the well-worn path of initially elated euphoria where enthusiasm holds sway over scientific evidence followed by critical scepticism with little optimism for the future. A period of criticial scientific evaluation is now needed, in which the lessons learned from the past are implemented. The initial experience has revealed three factors associated with complications: small vessels <3 mm, low blood flow with poor run off, and evidence of hypercoagulability or local thrombus formation. This has led most investigators to restrict the use of this stent to saphenous bypass grafts with large diameters and to the native circulation as 'bail-out' device. In Europe, according to the data from the Working group on endoluminal prostheses*, Medinvent stents have been implanted in 187 patients between March 1986 and June 1989 in both native coronary arteries and bypass grafts. Although stent implantation is capable of producing a superior haemodynamic result[19,25], the preliminary data suggest that the restenosis rate is between 15% and 30% according to the applied criteria (diameter stenosis $\geq 50\%$, $\geq 0{\cdot}72$ mm reduction in the minimal luminal diameter[52,53] [Fig. 4(a),(b)]. The Palmaz stent, currently used in three centres in Europe has been implanted in situations which are considered at low risk of acute problems, but at high risk of reocclusion (total occlusions, myocardium protected by collaterals). The intracoronary stent represents a 'double-edged sword': although the scaffolding properties of the device are attractive and of proven benefit it may provide an iatrogenic stimulus for erratic and uncontrolled cell proliferation. This potential has not been fully appreciated by the interventional cardiologist who may have opened a new

*Participating Centres and Collaborators: See appendix.

Pandora's box of complex biological interactions, but who may well be rescued by the cellular biologist in the future. The device is a logical vehicle for the topical release of agents that will ideally enhance endothelialization but suppress the keloid-type reaction of the traumatized vessel wall. Solution of this problem is not helped by the lack of joint effort on the part of the pharmaceutical industry and the industry producing the mechanical device. This is a source of frustration to investigators in the field, but hopefully will be overcome in the future. The initial hopes that stent implantation may prevent or diminish restenosis have not been fulfilled. In addition, early thrombotic occlusion in the native coronary circulation has led many temporarily to abandon this as an indication except for emergency 'bail-out' indications.

Are we sorcerer's apprentice?

A case report will illustrate our concern better than a long series of arguments. A male patient from Los Angeles, who had two major risk factors for CAD: diabetes and hypercholesterolaemia, sustained in 1977 an inferior myocardial infarction. Post infarction angina was treated by two saphenous vein grafts on an obtuse marginal and on a diagonal branch. Following recurrent angina he was reoperated upon and both internal mammary arteries were used to bypass the LAD and the RCA. Between 1984 and 1987 the vein graft on the left marginal artery was dilated on four occasions. In April 1987, his cardiologist referred the patient to Ulrich Sigwart in Lausanne for a stent implantation in both saphenous vein grafts. Seven months later, in November 1987, repeated dilatation was necessary within both stents. Five months later the patient again had restenosis; this time, a hot balloon angioplasty was considered but rejected by Richard Spears in Detroit (would the absorbed laser energy convert the stent into a 'hot roster'), and the first atherectomy inside the stent was performed by John Simpson in Palo Alto. In July 1988, the patient underwent a second atherectomy, which did not prevent restenosis. Disappointed by these results lasing with excimer laser (wavelength 308 nm) was successfully attempted in Los Angeles by Jim Forrester and his group[54]. Unfortunately for the patient, the stenotic lesion seemed to be more stubborn than the treating physicians and recurred once more. Tired of these multiple and varied interventions, the patient has decided for the time being to stay away from the sorcerer's apprentice and this long and thorny path has certainly brought down to earth the interventional cardiologist who has to face the unavoidable reality: in addition to a mechanical device a pharmacological approach will be necessary to achieve victory over restenosis.

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Appendix

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