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Editorial

I Like the Candy, I Hate the Wrapper

The ^{32}P Radioactive Stent

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United States patent 5059166, issued October 22, 1991, to Robert and Tim Fischell, described an "intraarterial stent with the capability to inhibit intimal hyperplasia."[1] The proponents of this patent went on to say in their proposal: "Since radiation from a radioisotope source is capable of selectively inhibiting the growth of hyperproliferating cells as compared with normal cells, a radioisotope material which forms part of the stent can be used to decrease the rate of arterial reclosure. The radioisotope could be placed inside the stent, alloyed into the metal from which the stent is made, or preferably, it can be coated onto the stent's exterior surface." So began the story of the radioactive stent. Eight years and several animal species later, we are becoming aware of the bright and dark sides of this treatment modality in the human model.

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The safety and efficacy study by Albiero and colleagues[2] describes the dose-related decrease noted at 6-month follow-up of intrastent neointimal hyperplasia after implantation of ^{32}P radioactive stents at activities of 0.75 to 12 μCi. Whereas in-stent restenosis was all but obliterated at higher doses of radiation, intralesion restenosis was high because of late lumen loss at the stent edges. Aptly, the authors coined the term "candy wrapper" to describe this new restenotic pattern. It is possible that the animal workers who implanted the first radioactive stents observed this phenomenon. Unfortunately, the significance of this finding may not have been immediately apparent.

Historical and Dosimetric Considerations

The study by Albiero and colleagues reflects the courage of the investigators who, despite indifferent and at times contradictory results from animal work, persisted in their endeavor to discover whether radioactive stent implantation would be effective in humans.

Previously, Hehrlein et al,[3,4] using the rabbit iliac model, polyisotopic ^{55}Co (elements ^{55}Co, ^{56}Co, ^{57}Co, ^{57}Ni, and ^{55}Fe) with activity levels of 17.5 and 35 μCi, and later ^{32}P stents (activity levels of 0.5, 4, 6, and 13 μCi), had demonstrated a dose-dependent effect of inhibition of neointimal hyperplasia within the stent. It had already been noted that lower activity levels were able to reduce neointimal hyperplasia, but the effect was lost at 12 weeks, particularly at the stent ends. Between struts and at stent ends, endothelialization occurred more rapidly and was dose-dependent.

In the porcine coronary restenosis model of Carter et al,[5] different activities of ^{32}P-containing stents were used. Mitchell[6] makes the following observation on these findings: "The doses delivered by the different activities of ^{32}P were divided into 3 categories: low ($<$2000 cGy), intermediate (4000 cGy) and high ($>$10 000 cGy). Based on these values, the average dose rates to the tissue over the 25-day period of the study were: low (3 cGy/h), intermediate (6 cGy/h), and high (15 cGy/h). It is interesting that both the high and low doses and dose rates were effective in reducing the extent of restenosis, whereas, the intermediate dose/dose rate was ineffective if not worse than the control. These findings do not conform to the findings that would be expected as dose and dose-rate are reduced. One might expect the high dose/dose rate to be effective and perhaps the intermediate and low dose/dose rate to be ineffective. The fact that the low dose/dose rate treatment was effective in this study suggests that perhaps an inverse dose-rate effect is operative over a narrow range of dose rates in this model." As suggested above, it is not only the total dose of irradiation delivered to the tissue that is important but also the dose-rate time interval in which radiation is delivered. This reflects the simultaneous processes of DNA repair, concurrent with the damage induced by radiation exposure. This is particularly important in comparisons of the high dose-rates of catheter-based techniques with those of radioactive stents that use low dose-rates. An increase in the dose-rate at which certain cell lines are irradiated in vitro demonstrates a killing effect that is most marked between 1 and 100 cGy/min.[4,7] However, at 0.6 cGy/min, there is more effective cell killing than at 0.2 or 2.6 cGy/min. This is due to cell cycle blockade. At this dose-rate, the cells are selectively blocked at G_2/mitosis, a more radiosensitive phase of the cell cycle. Once this occurs, the low-dose-rate treatment becomes much more efficient with respect to killing (inverse dose-rate effect).[6]

We previously made the following comment on these conflicting observations: "so far incremental doses have always resulted in more cell death or decreased cell proliferation. We cannot exclude that there is a U-shaped dose-response curve for endovascular radiation, but in view of all the earlier reports, this is unlikely."[8] Of course, it is possible that the European rabbit was more receptive to the effects of brachytherapy than the American pig. In general, the results derived from certain animal testing and the dose-finding

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effect in human series of Albiero et al appear logical and are in keeping with the general rule of brachytherapy: the more you irradiate, the more you inhibit proliferation, up to the point at which detrimental effects appear.

Recently, more information has become available on the delayed endothelialization of the radioactive stent,[9] with the consequent risk of late thrombosis. Albiero and colleagues endeavored to avoid the thrombotic sequelae of late endothelialization by using longer courses of antiplatelet agents. We are aware of only 1 episode of subacute thrombosis occurring in humans after radioactive stent implantation to date, in contrast to recent findings using the combination of conventional stents and catheter-based radiation.[10,11]

Not All Radioactive Stents Are Equal: Techniques of Stent Activation

The clinical effect of a radioactive stent may be modulated by use of radioisotopes with different half-lives, energy, activity, and penetration. Consequently, in the interpretation of results originating from different radioactive stent trials that used different isotopes, extrapolation between stents and isotopes may be inappropriate. The trials discussed above used 2 different techniques to make the stents radioactive: (1) direct ion implantation (that used by Isostent to create the ^{32}P stent) (Isostent Inc, Belmont, Calif, personal communication): phosphorus-containing ^{32}P isotope produced by neutron activation was inserted into the ion source of an implanter. Ionized ^{31}P and ^{32}P atoms were accelerated and separated by a magnet so that only the ^{32}P was implanted directly onto the stent surface. (2) Bombardment with charged particles (as used by Hehrlein et al)[3,4]: the stents were placed into a cyclotron and bombarded with deuterons. Metallic stent particles were transformed into several radioisotopes. Later, proton bombardment was used to reduce the high-energy γ-radiation emitted by the stents.

Other methods currently available include electrodeposition (a technique for the manufacture of a γ-radiation–emitting stent) and finally, isotope-emitting gold and phosphorylcholine stents. Clear advantages of 1 technique over another will be the subject of future consumer reports.

The ^{32}P Stent: An Antirestenotic Stent Using an Electron-Beam Fence

In our enthusiasm to control vessel recoil and remodeling after balloon angioplasty, stent implantation has become increasingly popular. With conventional stenting, we have eliminated recoil and remodeling as components of the restenotic process. However, this has been at the cost of exacerbating neointimal proliferation secondary to chronic vessel wall irritation, leading to in-stent restenosis.[12]

As a means of preventing neointimal proliferation, the idea of creating an electron-beam fence has been raised. Simply, the idea is to place radioactivity where it should be in the first place: at the endoluminal surface, generating a fence that should "fry" any smooth muscle cells or myofibroblasts trying to reach the endoluminal cavity created by the stent.[13] In this model, the concept of irradiating a target volume, as is desirable with cancer or catheter-based technologies, may not be relevant. Catheter-based brachytherapy involves the use of a single-hit, high-dose administration of intracoronary radiation. It seeks to target a volume of myofibroblasts and smooth muscle cells within the adventitia by irreversibly altering the DNA, such that on cell division, death will occur. This clearly decreases the reproductive capacity of the adventitia as a unit, and consequently, the potential for restenosis. Using the radioactive stent approach, we do not have to neutralize the huge reservoir of quiescent myofibroblasts lying dormant in the adventitia. Prevention of the migration and invasion of myofibroblasts occurs because of the continuous and low dose-rate, as witnessed by Albiero et al, adding credence to the concept of the electron-beam fence. This takes place regardless of the bulk of the atherosclerotic plaque and extent of penetration of the radiation. Equally, it occurs despite the eccentric placement of the radioactive stent within the vessel. In a preliminary report, the Milan group[14] demonstrated that a heterogeneous adventitial exposure (maximum dose, 4378±3078 cGy/14 d; minimum dose, 563±360 cGy/14 d; range, maximum dose, 644 to 12 210 cGy/14 d; range, minimum dose, 153 to 1461 cGy/14 d) still results in a homogeneous stent response with respect to the formation of neointimal hyperplasia.

Initially, basic scientists and radiotherapists perceived the concept of an electron-beam fence as being a fantasy created by cardiologists, objecting that it was not realistic. Ultimately, however, the proponents of the fence may just be correct.

Application of the concept of an electron-beam fence to the stent edge, however, makes one aware of its potential Achilles' heel. The range of the stent radioactivity is limited, and whereas those cells behind the stent struts may be well fenced at the doses discussed, cells proximal and distal to the extremity of the stent, in injured areas treated by the balloon (up to 3 mm outside the stent; personal communication, Isostent), may not be effectively covered by the range of the stent radiation. The latter phenomenon has been described in radiotherapeutic terms as "geographical miss": the mismatch between the irradiated and injured area[15] (Figure 1).

The Problem of the Candy Wrapper and Its Prevention: Is the Candy Wrapper Another Oculostenotic Illusion?

Stent-edge renarrowing occurs after conventional stent implantation.[16] This may not be angiographically visible, because the luminal ingrowth at the stent edges is in juxtaposition to the neointimal hyperplasia within the stent, producing a smooth contour on the luminogram. In contrast, after radioactive stenting, a visual gradient at the extremities becomes apparent, because nothing will grow within the stent, which makes all edge restenoses obvious.

In the study by Albiero et al, we note that lesions received a further percutaneous intervention on the basis of whether there was evidence of >50% intralesion angiographic stenosis. It may be that a word of caution is required in the assessment of the stent-edge lesion so as not to be seduced into believing that all such stenoses require treatment, given that the transition from the pristine stent lumen to the stent edge may appear great.

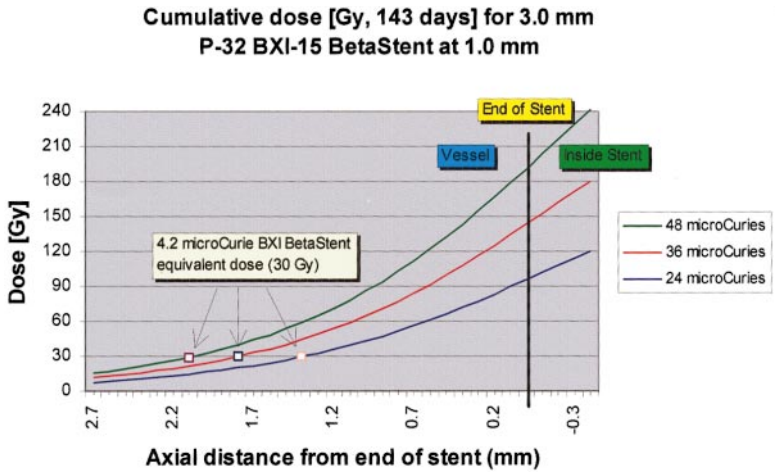

Figure 1. Dose representation for a 3.0-mm-diameter P-32 BX Isostent with activity level 4.2 μCi measured at 1 mm from stent struts. *y* axis: Total dose to tissue in Gy. *x* axis: Vertical line represents edge of stent. Area to right of vertical line is within stent. Area proximal (or distal) to stent is depicted to left of vertical line. Maximal balloon overhang is described to a total of 2.7 mm axially. Each isodose curve describes dose delivered to tissue by stents of different activity levels (24, 36, and 48 μCi), both within and proximal/distal to stent. Model assumes that a dose of 30 Gy is required to inhibit neointimal proliferation. Note that as stent activity decreases, dose delivered to tissue proximal/distal to stent is no longer sufficient to cover area injured by balloon.

The propensity for edge restenosis to occur at either the proximal, distal, or both edges also remains ill-defined. It is conceivable that after conventional stenting, stent-edge restenosis with luminal narrowing adjacent to a pristine stent lumen could result in a rheological condition with consequent alteration of shear stress, promoting what is finally viewed as a candy wrapper.

Identifying the mechanism by which the candy wrapper occurs may permit a more focused strategy concerning its treatment. Using intravascular ultrasound, the authors describe an increase in plaque/media in the region 1 to 3 mm immediately proximal and distal to the stent and a decrease in the external elastic membrane from 4 to 10 mm. To combat these identified vascular changes that induce stent-edge restenosis, various modifications to existing radioactive stent morphology could be proposed: (1) the square-shouldered balloon, (2) the cold-end stent, (3) the hot-end stent, (4) a hybrid radioactive stent/radioactive catheter–based system, (5) a self-expanding radioactive stent, and finally (6) the γ-stent.

The appropriateness of any one of these suggestions will depend on what underlies the change in plaque volume and/or shrinkage in vessel size. As usual in medicine, the problem is likely to be multifactorial, with confounding factors. At first sight, the elements may be portrayed schematically as in Figure 2.

Is the edge effect secondary to low-dose radiation at the margins of the stent, or due to balloon injury at the stent edges, or a combination of the 2? In this study, the univariate analysis suggests that those vessels with a higher final balloon-to-artery ratio, smaller reference lumen diameter, and smaller final minimum lumen diameter by angiography are most susceptible to adverse stent-edge morphological change.

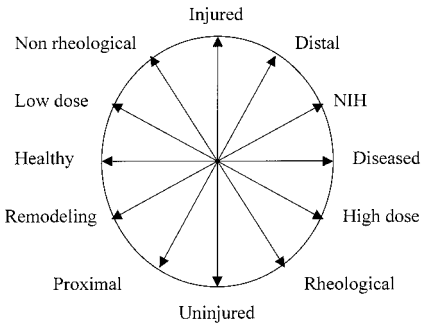

Figure 2. Multifaceted interaction that creates candy wrapper.

If the edge effect is the result of balloon-induced trauma and low-dose radiation (Figure 3A), then limiting the trauma outside the stent and expanding the irradiated area beyond the injured area should be attempted. Conceivably, the most practical approach may be to use a square-shouldered balloon (to minimize the injured area outside the stent) in combination with an extension of the area of irradiation beyond the injured area ("hot-end stent") (Figure 3B).

If the candy wrapper were purely the result of negative remodeling induced by low-dose radiation in an injured area, then the lengthening of the stent by a nonradioactive, cold-end stent would be a logical solution to prevent remodeling at the extremities (Figure 3C). If plaque constitutes a large percentage of the healing process manifested by the candy wrapper, then cold-end stent implantation is unlikely to work. Similarly, neointimal proliferation may occur at the edges of the radiation within the stent if this treatment modality is used.

A more elaborate, sophisticated approach would be the hybrid combination of a radioactive stent with the use of catheter-based radiation. The sources could be incorporated on the shaft of the balloon at the balloon extremities (Figure 3D). This approach would ensure that the injured area receives appropriate radiation.

If the candy wrapper is the result of an aberrant response by noninjured healthy or diseased tissue subjected to radiation, then this may suggest that low-dose radiation has a stimulatory effect on noninjured tissue.[17] This would be the worst possible scenario, because clearly, noninjured healthy or diseased tissue will always be irradiated at some stage.

In the event that excessive vascular remodeling is present after hot-ended or hybrid therapy, then a self-expanding nitinol radioactive stent may play a useful role (Figure 3E).

The γ-stent would have better tissue penetration than the β-emitting rivals. However, the energy generated by the former will be a drawback, with increased radiation exposure to patients, relatives, and personnel. It is conceivable that a low-energy, γ-radiation–emitting stent would minimize this

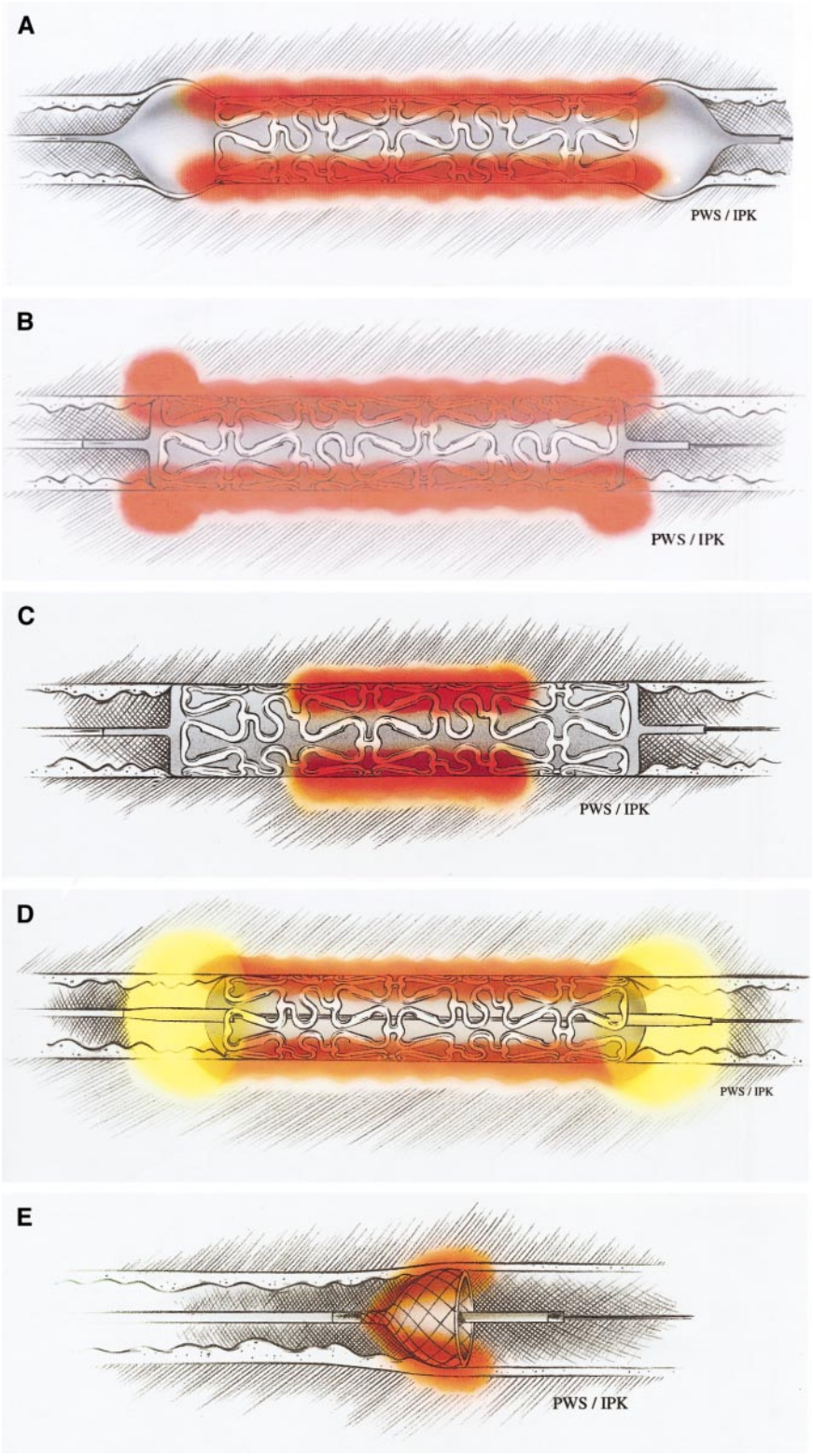

Figure 3. A, Illustration of a balloon-expandable BX stent. Radiation is depicted in orange. Note that trauma to vessel wall extends beyond that of radiation. B, Square-shouldered balloon limits area of injury, whereas radiation from hot-ended stent extends to normal/uninjured tissue. C, Cold-end stent with radiation limited to central area. D, Hybrid radioactive stent with catheter-based sources at each end to ensure that injured area receives adequate radiation coverage. E, Self-expanding radioactive nitinol stent.

environmental risk, yet provide adequate clinical effect. Further scientific exploration of this area is clearly justified.

Conclusions

Although a decade has elapsed since the inception of radioactive stenting, we are now beginning to understand that this treatment modality is indeed a double-edged sword. The path of evolution is clearly a slow one; meticulous work has been performed to clarify the efficacy of the radioactive stent. Albiero and colleagues have pointed us in a new direction, beyond the stent itself, and that is to carefully analyze the effect of injury and low-dose radiation on vessel healing at the stent edge. The true sweetness of the candy will only be appreciated once the pathophysiology of stent-edge restenosis is understood.

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