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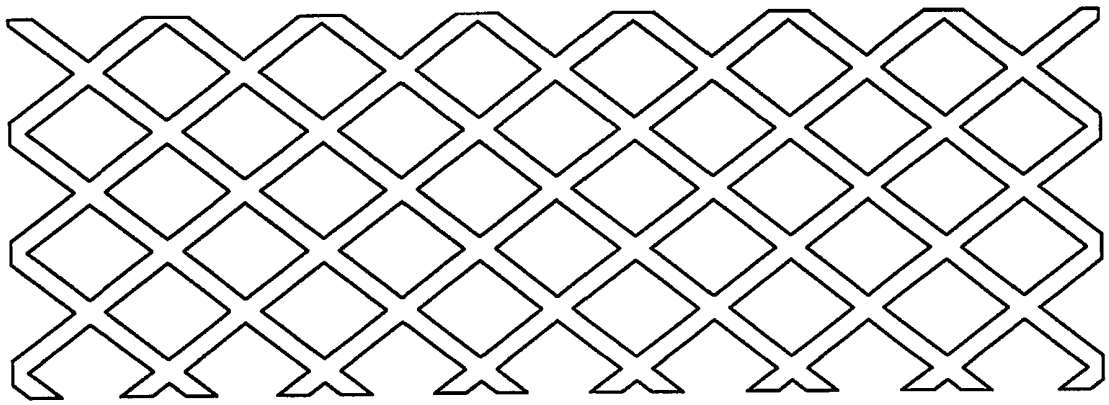

(57) Abstract

This invention is a radiation delivery source (1) which may be used to deliver a radioactive dose to a site in a body lumen. The source comprises a substrate (10) in the form of a stent (unnumbered), to which is attached a layer (12) of relatively insoluble metal salt which includes at least one radioisotope. Optionally, the source (1) may further include a coating (14) which seals the source.

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RADIOACTIVE STENT

Field of the Invention

This invention relates to the field of medical devices in general, and coronary and peripheral stents for intravascular radiation therapy in one particular application.

Background of the Invention

PTA treatment of the coronary arteries, percutaneous transluminal coronary angioplasty (PTCA), also known as balloon angioplasty, is the predominant treatment for coronary vessel stenosis. Approximately 300,000 procedures were performed in the United States in 1990 and nearly one million procedures worldwide in 1997. The U.S. market constitutes roughly half of the total market for this procedure. The increasing popularity of the PTCA procedure is attributable to its relatively high success rate, and its minimal invasiveness compared with coronary by-pass surgery. Patients treated by PTCA, however, suffer from a high incidence of restenosis, with about 35% or more of all patients requiring repeat PTCA procedures or by-pass surgery, with attendant high cost and added patient risk.

More recent attempts to prevent restenosis by use of drugs, mechanical devices, and other experimental procedures have had limited long term success. Stents, for example, dramatically reduce acute reclosure, and slow the clinical effects of smooth muscle cell proliferation by enlarging the minimum luminal diameter, but otherwise do nothing to prevent the proliferative response to the angioplasty induced injury.

Restenosis is now believed to occur at least in part as a result of injury to the arterial wall during the lumen opening angioplasty procedure. In some patients, the injury initiates a repair response that is characterized by hyperplastic growth of the vascular smooth muscle cells in the region traumatized by the angioplasty. Intimal hyperplasia or smooth muscle cell proliferation narrows the lumen that was opened by the angioplasty, regardless of the presence of a stent, thereby necessitating a repeat PTCA or other procedure to alleviate the restenosis.

Preliminary studies indicate that intravascular radiotherapy (IVRT) has promise in the prevention or long-term control of restenosis following angioplasty. IVRT may also be used to prevent or delay stenosis following cardiovascular graft procedures or other trauma to the vessel wall. Proper control of the radiation dosage, however, appears to be important to inhibit or arrest hyperplasia without causing excessive damage to healthy tissue. Overdosing of a section of blood vessel can cause arterial necrosis, inflammation, hemorrhaging, and other risks discussed below. Underdosing will result in inadequate inhibition of smooth muscle cell hyperplasia, or even exacerbation of hyperplasia and resulting restenosis.

The prior art contains many examples of catheter based radiation delivery systems. The simplest systems disclose seed train type sources inside closed end tubes. An example of this type of system can be found in U.S. Patent No. 5,199,939 to Dake. In order to separate the radiation source from the catheter and allow re-use of the source, a delivery system is disclosed by U.S. Patent No. 5,683,345 to Waksman et al. where radioactive source seeds are hydraulically driven into the lumen of a closed end catheter where they remain for the duration of the treatment, after which they are pumped back into the container. Later disclosures integrated the source wire into catheters more like the type common in interventional cardiology. In this type of device, a closed end lumen, through which is deployed a radioactive source wire, is added to a conventional catheter

construction. A balloon is incorporated to help center the source wire in the lumen. It is supposed that the radioactive source wire would be delivered through the catheter with a commercial type afterloader system produced by a manufacturer such as Nucletron, BV. These types of systems are disclosed in Liprie 5,618,266, Weinberger 5,503,613, and Bradshaw 5,662,580.

In the systems disclosed by Dake and Waksman, the source resides in or very near the center of the catheter during treatment. However, it does not necessarily reside in the center of the artery. The systems disclosed by Weinberger and Bradshaw further include a centering mechanism, such as an inflatable balloon, to overcome this shortcoming. In either case, the source energies must be high enough to traverse the lumen of the blood vessel to get to the target tissue site in the vessel wall, thus requiring the use of higher energy sources. Higher energy sources, however, can have undesirable features. First, the likelihood of radiation inadvertently affecting untargeted tissue is higher because the absorption factor per unit tissue length is actually lower for higher energy radiation. Second, the higher energy sources are more hazardous to the medical staff and thus require additional shielding during storage and additional precaution during use. Third, the source may or may not be exactly in the center of the lumen, so the dose calculations are subject to larger error factors due to non-uniformity in the radial distance from the source surface to the target tissue. The impact of these factors is a common topic of discussion at recent medical conferences addressing Intravascular Radiation Therapy, such as the Trans Catheter Therapeutics conference, the Scripps Symposium on Radiotherapy, the Advances in Cardiovascular Radiation Therapy meeting, the American College of Cardiology meeting, and the American Heart Association meeting.

The impact on treatment strategy is discussed in detail in a paper discussing a removable seed system similar to the ones disclosed above (Tierstein et al., Catheter based Radiotherapy to Inhibit Restenosis after Coronary Stenting, NEJM 1997; 336(24):1697-1703). Tierstein reports that Scripps Clinic physicians inspect each vessel using ultrasonography to assess the maximum and minimum distances from the source center to the target tissue. To prevent a dose hazard, they will not treat vessels where more than about a 4X differential dose factor (8-30 Gy) exists between the near vessel target and the far vessel target. Differential dose factors such as these are inevitable for a catheter in a curvilinear vessel such as an artery, and will invariably limit the use of radiation and add complexity to the procedure. Moreover, the paper describes the need to keep the source in a lead transport device called a pig", as well as the fact that the medical staff leaves the catheterization laboratory during the treatment. Thus added complexity, time and risk is added to the procedure caused by variability of the position of the source within the delivery system and by the energy of the source itself.

In response to these dosimetry problems, several more inventions have been disclosed in an attempt to overcome the limitations of the high energy seed based systems. These systems share a common feature in that they attempt to bring the source closer to the target tissue. For example, U.S. Patent No. 5,302,168 to Hess teaches the use of a radioactive source contained in a flexible carrier with remotely manipulated windows; Fearnot discloses a wire basket construction in U.S. Patent No. 5,484,384 that can be introduced in a low profile state and then deployed once in place; Hess also purports to disclose a balloon with radioactive sources attached on the surface in U.S. Patent No. 5,302,168; Hehrlein discloses a balloon catheter coated with an active isotope in WO96/22121; and Bradshaw discloses a balloon catheter adapted for use with a liquid isotope

in U.S. Patent No. 5,662,580. The purpose of all of these inventions is to place the source closer to the target tissue, thus improving the treatment characteristics.

In a non-catheter based approach, U.S. Patent No. 5,059,166 to Fischell discloses an IVRT method that relies on a radioactive stent that is permanently implanted in the blood vessel after completion of the lumen opening procedure. Radiation delivery systems provided on a stent have also been disclosed in U.S. Patent No. 5,176,617 to Fischell et al., , and in U.S. Patent No. 5,674, 177 to Heirlein et al.. The use of a stent as a platform is of particular interest because it has been shown to be effective in animals, even at activity ranges as low as 0.14-0.23 μCi (microcuries). Refer, for example, to Fischell, et al., Low-Dose, β-Particle Emission From Stent Wire Results in Complete, Localized Inhibition of Smooth Muscle Cell Proliferation", Circulation, vol. 90, pp. 2956-2963, (1994); Laird et al, Inhibition of Neointimal Proliferation with Low-Dose Irradiation From a β-Particle-Emitting Stent", Circulation, 93:529-536 (1996); Carter, et al, Effects of Endovascular Radiation From a β-Particle Emitting Stent in a Porcine Coronary Restenosis Model [A Dose-Response Study], Circulation 92:1570-1575 (1995); and Hehrlein, et al, Pure β-Particle-Emitting Stents Inhibit Neointima Formation in Rabbits", Circulation 93:641-645 (1996).

Several limitations exist in the systems disclosed in the literature and in the currently available art. One limitation is that the isotope chosen for the radiation is dependent on the materials used for the stent. For example, in the systems described in Fischell '617 and '166, Hehrlein '177, and in the stents used in the experiments described by Fischell and Hehrlein in their 1995 papers cited above, the active isotopes were limited to species created by direct neutron activation of the stent in a reactor. This process limits control over the type and amount of radiation that the stent can possess. Hehrlein '177 discloses no less than nine different isotopes created by this process, each with its own half-life, activity level, and radiation characteristics. This set up makes control over the radiation dose extremely difficult, and investigation into the interaction of the radiation with tissue very problematic.

To overcome this limitation, the stents used in the study described by Laird were made by first ion implanting the stent with phosphorous-31 (P-31 or ^{31}P), then placing the stents in a reactor to convert the stable P-31 to the beta-emitting P-32. Alternatively, the radioactive stent described in Fischell '166 and '617 describe coating or otherwise encapsulating a cold version of the target isotope in the stent material, and then placing the stent in a reactor to convert the stable isotope to a radioactive one. This approach, while offering some improvement over the prior method, is limited in the total activity attainable. For example, consider the activation of P-32 by neutron bombardment. Only about 1 in every 100,000 P-31 ions is converted to P-32 in the reactor chamber over a 10-day period. While this conversion rate can be increased, there is a physical limitation to this process dictated by the reactor flux, the cross section of the target atom, and the half-life of the isotope. Moreover, this method does not completely eliminate the activation of non-desired isotopes created from the stent material.

To further reduce the radiation emitted from the stent to a single isotope, Hehrlein describes the use of direct ion implantation of active P-32 in his paper "Pure β-Particle-Emitting Stents Inhibit Neointima Formation in Rabbits" cited previously. While successfully providing a single mode of radiation using this method, the ion implantation process presents other limitations. For example, ion implantation is only about 10 to 30% efficient. In other words, only about one in every ten ions put into the accelerator is implanted on the target, the remainder remains in the machine. Thus, the radiation level of the

machine increases steadily with consistent use. With consistent use, the machine can become so radioactive that it must be shut down while the isotope decays away. Therefore, the isotope used must be of a relatively short half-life and/or the amount of radiation utilized in the process must be very small, in order to shorten the "cooling off" period. Moreover, the major portion of the isotope is lost to the process, implying increased cost to the final product.

Notwithstanding the foregoing, there remains a need for a radioactive stent having an improved attachment between the radioisotope and the stent. Preferably, the attachment mechanism will accommodate both gamma and beta sources, and be adaptable to a wide variety of stent materials.

Summary of the Invention

There is provided in accordance with one aspect of the present invention, a radiation delivery source in the form of a stent. The source comprises a substrate layer in the form of a stent and an isotope layer. The isotope layer comprises a metal salt or metal oxide, and at least one isotope. Preferably, the isotope is selected from the group of gamma emitters with energies less than about 300 keV including I-125, Pd-103, As-73, and Gd-153, or the high energy beta group ($E_{max} > 1.5$ meV) including P-32, Y-90 and W/Re-188. Other isotopes not currently mentioned, can be utilized by the invention described herein. The selection of these isotopes, however, allows the source to be shielded in a material such as leaded acrylic in commercially available thickness of 15-30 mm, or in a lead tube of approximately 0.3-0.5 mm wall thickness. Some of the other isotopes which may be deemed suitable for use in the present invention or for a particular intended use, include Au-198, Ir-192, Co-60, Co-58, Ru-106, Rh-106, Cu-64, Ga-67, Fe-59, and Sr-90. The selection of an isotope may be influenced by its chemical and radiation properties.

In one embodiment, the radiation delivery source further comprises an outer coating layer. The coating layer may comprise any of a variety of materials such as cyanoacrylates, acrylics, acrylates, ethylene methylacrylate acrylic acid, urethanes, polyvinylidene chloride (PVDC, such as Saran®), polybutyl vinyl chloride (PBVC), other polymers, and combinations thereof. The outer coating layer may also comprise biocompatible materials such as heparin.

In accordance with a further aspect of the present invention, there is provided a radiation delivery source in the form of a stent, comprising a substrate in the form of a stent, an isotope layer, and a tie layer which lies between the isotope layer and the substrate. The isotope layer comprises a relatively insoluble salt of at least one isotope, as discussed above. In one embodiment, the tie layer comprises a metal, metal oxide, metal salt or alloy. In another embodiment, the radiation delivery source also comprises an outer coating layer, preferably comprising materials discussed above.

In accordance with a further aspect of the present invention, there is provided a method for making a radiation delivery source in the form of a stent. The method comprises the steps of providing substrate in the form of a stent, and coating the substrate with an isotope layer comprising a relatively insoluble salt of at least one isotope. In one embodiment, the coating step comprises the steps of coating the substrate with at least one layer of metal, reacting the layer of metal to form a metal oxide or metal salt, and exposing the layer of in the metal oxide or metal salt to a fluid comprising a plurality of isotope ions to form the isotope layer. In another embodiment, the coating step comprises the steps of coating the substrate with a

layer of metal salt, and exposing the layer of metal salt or oxide to a fluid comprising a plurality of isotope ions to form the isotope layer. In one embodiment, the method further comprises the step of coating the isotope layer with a coating layer.

In accordance with another aspect of the present invention, there is provided a method of treating a site within a vessel. The method comprises the steps of identifying a site within a vessel to be treated, providing a radiation delivery source of the present invention, positioning the source within the treatment site, and deploying the source at the treatment site.

Brief Description of the Drawings

FIGURE 1 is a view of an embodiment of the radiation delivery source of the present invention.

FIGURE 2A is a schematic of a cross-section of one embodiment of the radiation delivery source of the present invention having a substrate layer and an isotope layer.

FIGURE 2B is a schematic of a cross-section of one embodiment of the radiation delivery source of the present invention having a substrate layer, an isotope layer and a coating layer.

FIGURE 2C is a schematic of a cross-section of one embodiment of the radiation delivery source of the present invention having a tie layer disposed between the substrate layer and the isotope layer.

FIGURE 2D is a schematic of a cross-section of one embodiment of the radiation delivery source of the present invention having a substrate layer, a tie layer, an isotope layer and a coating layer.

FIGURE 3A is a schematic of a cross-section of one embodiment of the radiation delivery source of the present invention having a substrate layer and an isotope layer.

FIGURE 3B is a schematic of a cross-section of one embodiment of the radiation delivery source of the present invention having a substrate layer, an isotope layer and a coating layer.

FIGURE 3C is a schematic of a cross-section of one embodiment of the radiation delivery source of the present invention having a tie layer disposed between the substrate layer and the isotope layer.

FIGURE 3D is a schematic of a cross-section of one embodiment of the radiation delivery source of the present invention having a substrate layer, a tie layer, an isotope layer and a coating layer.

The drawing figures are not necessarily to scale.

Detailed Description of the Preferred Embodiments

This invention provides a novel radiation delivery source, new in terms of materials and production methods. The invention can be generally described as a radioactive source intended for site specific delivery of radiation ("brachytherapy") to an anatomical structure. The source is intended for incorporation into a stent, such as an intraarterial stent. The present invention also provides a method for permanently attaching a radioactive isotope to a stent substrate without the usual limits caused by the half-life or activity of the isotope. The invention further provides a method by which an isotope can be attached to a substrate that does not generate excessive radioactive waste as a by-product of production.

The radiation delivery sources of the present invention are devices which allow for the intraluminal placement or implantation of a source of radiation which is securely bound to the stent substrate. Referring to Figure 1, the radiation delivery source 1 is based upon a stent, which serves as a substrate for supporting the radioisotope, as well as performing the normal

functions of a stent as are known in the art. The source 1 may be anywhere from about 5 mm to 100 mm in length, depending upon the length of lesion to be treated. Many stents are within the range of from about 15 mm to about 40 mm. Diameters are generally from about 2.0 mm to 20 mm, depending upon the application. Radioactive stents intended for the coronary arteries will generally be within the range of from about 2.0 mm to about 4.0 mm.

The radiation delivery sources of the present invention are comprised of two or more layers of materials. There may or may not be a clear visual or physical distinction between the various layers in the source 1 because each layer need not be a discrete structural element of the source 1. As the layers bond together to form the source, they may become blended, alloyed or intermingled to form what looks and acts like a single layer having a somewhat heterogeneous composition. For this reason, the various layers as defined and used herein are intended to denote the functional characteristics of the components or help denote what process steps are used in their formation, whether through the use of discrete structural layers or layers blended with neighboring layers, the selection of which will be apparent to those of skill in the art in view of the particular materials and components used.

The radiation delivery sources of the present invention all comprise a substrate layer or substrate 10. The substrate 10 may be any of a variety of implantable prosthetic devices, particularly those commonly referred to as stents or grafts. Any of a variety of commercially available stents can be coated with a radioactive isotope in accordance with the disclosure herein, or stents can be specially constructive for the purpose of carrying a radioisotope, in which the surface area of the stent in contact with the vessel wall can be optimized for the radiation delivery purposes. Examples of currently available stents which can be coated using the technology disclosed herein include the NIR and Radius nitinol stents (Boston Scientific); GFX (Arterial Vascular Engineering) Palmaz-Schatz and Crown (Johnson & Johnson/Cordis); Multi-link (Guidant); Wiktor (Medtronic) and GR2 (Cook) among others. Self expandable stents of the rolled sheet type may also be provided with a radioactive coating in accordance with the present invention. This includes, for example, United States Patent No. RE 35988 entitled Stent Construction of Rolled Configuration to Winston et al. and United States Patent No. 5,728,150 issued March 17, 1998 entitled Expandable Microporous Prosthesis to McDonald, the disclosure of which are incorporated in their entireties herein by reference.

Alternatively, the substrate may comprise any of a variety of non-stent structures such as pins, needles, seeds or other devices which may be useful for percutaneous or surgical insertion into either tissue or body cavity or potential cavities. For example, probes for insertion into soft tissue such as to treat tumors may be provided with a radioactive source in accordance with the present invention.

Whether the substrate comprises a stent or other structure, or the surface layer on a stent or other structure, the substrate may comprise any of a variety of materials. Examples of common materials for current stents and probes to which the radioisotope of the present invention may be attached include various alloys of stainless steel, nitinol, ELGILOY, gold, platinum or others which will be recognized by those of skill in the art. Nonmetallic surfaces which may be provided with an isotope in accordance with the pretreatment and attachment aspects of the present invention include any of the wide variety of materials well known in the medical arts. For example, PEBAX, polytetrafluoroethefene, various densities of polyethylene, polyethylene terephthalate, and nylon are among those most commonly used. Persons of ordinary skill in the art will appreciate

how to adapt the binding chemistry of the present invention to these and other materials in accordance with the disclosure herein.

The radiation delivery sources also all comprise an isotope layer 12. The isotope layer 12, comprises metal salt wherein a plurality of the ions in the salt are radioisotopes. The radioisotope can be almost any species available, preferably beta or gamma emitting, as is discussed below. The isotope layer 12 may further comprise one or more metals from which the metal salt of the layer is derived. The isotope layer preferably has an isotope density or nuclide density in the range of 10^{10}-10^{25} atoms/cm^2, more preferably about 10^{13}-10^{15} atoms/cm^2 more preferably about 10^{14} atoms/cm^2 and has a thickness of preferably 100-10,000 Angstroms thick, more preferably about 500-1500 Angstroms thick.

As used herein, the term "metal salt" refers to a compound comprised of at least one anion and at least one cation. The anions and cations of the metal salt may be either simple (monatomic) ions such as Al^{3+}, Cl^- and Ag^{1+}, or complex (polyatomic) ions such as PO_4^{3-} and WO_4^{2-}. At least one of the ions in the metal salt compound should comprise a metal. The term "metal" as used herein means all metals, including, for example, semimetals, alkali metals, and alkaline earth metals. Preferably metals are selected from the transition metals or main group of the Periodic Table of the Elements. The term "metal salt" as used herein in its broadest sense can encompass metal oxides.

The radiation delivery sources of the present invention may further comprise a tie layer 11. The tie layer 11 lies between the substrate 10 and isotope layer 12 and may act to increase the tenacity of attachment of the isotope layer 12 to the substrate 10. The tie layer 11 may comprise adhesives, chemically activated surfaces, a chemical coating layer, an organic or inorganic compound, a metal, metal salt or metal oxide. Preferably the tie layer 11, is 100 to 10,000 Angstroms thick, more preferably 200 to 500 Angstroms.

The radiation delivery sources of the present invention may further comprise one or more coating layers 14. The coating layer 14, may act as a sealing means to protect the isotope layer from mechanical abrasion or other injury which may strip the isotope layer of radioisotopes and thus reduce its activity. Furthermore, the coating layer may inhibit migration or other leaking of isotope in an aqueous (blood) environment. Addition of a coating layer may provide sufficient protection for the device to be classified as a sealed radiation source, i.e. one that has less than 5 nCi of removable activity. Each coating layer is preferably 1 μm to 30 μm, more preferably 10 μm to 20 μm.

The coating may be a metal or plastic. Plastic coating materials are preferably biocompatible, but not excessively biodegradable. Preferred materials include cyanoacrylates, acrylics, ethylene methyl acrylate, ethylene methyl acrylate/acrylic acid (EMA/AA), urethanes, thermal plastic urethane (TPU), PBVC, PVDC, polyethylene, polyethylene terephthalate, nylon, and the like. Metal coatings can be used as well, with metals used preferably being bio-stable, such as titanium. For example, platinum, gold, or titanium may be vapor deposited on a surface to encapsulate the isotope layer.

The shape of the source is generally dictated by the geometry of the substrate 10. Some preferred substrates are: (1) a stent formed from a metal foil or sheet, preferably having a generally rectangular cross-section; (2) a stent formed from bent wire, preferably having a generally round cross-section; and (3) a stent cut from a metal tube. When present, any of the above-

described layers, other than the substrate, are disposed over at least one surface of the source, and may be disposed over the entire surface of the source. All layers present in a given embodiment need not cover the same areas of the substrate.

Figures 2A-2D and 3A-3D show several different preferred embodiments of the radiation delivery source of the present invention. Figures 2A-2D depict sources having a generally rectangular cross-section wherein the layers other than the substrate 10 are disposed on the outer surface of the source only, that which would be in contact with the tissue which forms the wall of the lumen. Figures 3A-3D depict sources having a generally circular cross-section wherein the layers are disposed over the entire surface of the substrate 10.

Referring to Figures 2A and 3A, schematics of cross-sections of two-layer embodiments of radiation delivery sources are shown. The first or innermost layer is the substrate 10, and the second or outer layer is the isotope layer 12.

Referring to Figures 2B and 3B, schematics of cross-sections of radiation delivery sources, wherein the sources have three layers, are shown. The first or innermost layer is the substrate 10, the second or middle layer is the isotope layer 12, and the outer layer is the coating layer 14.

Referring to Figures 2C and 3C, schematics of cross-sections of three-layer embodiments of the radiation delivery sources are shown, which are different from the three-layer embodiments disclosed above. The first or innermost layer is the substrate 10, the second or middle layer is the tie layer 11, and the outer layer is the isotope layer 12.

Referring to Figures 2D and 3D, schematics of cross-sections of four-layer embodiments of the radiation delivery sources of the present invention are shown. The four layers are the substrate layer 10, tie layer 11, isotope layer 12, and coating layer 14.

Some of the difficulties associated with a lack of consistent dosing which is found with radiation delivery stents of the prior art, as discussed above, could be overcome through the use of longer half-life isotopes. Compared to the example above wherein three stents were implanted with P-32 to a level of 10μCi using the Hehrlein method resulting in a dose variation of 29% at 7 days and 50% at 14 days, for stents implanted with an isotope with a 60-day half-life, the dose variation between maximum and minimum over the fourteen-day time frame would be reduced to 15%, and over a 7-day period to just 8%. The total dose for the longer half-life isotope will be greater, however the effective dose and dose rate remains to be determined. It is generally known that radiation dose can be increased if it is fractionated, or given over extended periods. Only experimentation can answer this question. However, if a long half-life isotope eventually proves effective, the lowest amount of radiation required to perform treatment is always preferable to any higher amount for safety reasons.

In general, the desired dose appears to be at least about 40 Gray within the first five half-lives of implantation, delivered to a depth of about 1 mm into the vessel wall, or about 20 Gray delivered to a depth of about 0.5 mm into the vessel wall, along the entire length of the source. That implies an activity of about 1 microCurie per centimeter length of stent. The dose may range as high as about 500 Gray at a depth of about 0.5 mm in five half-lives of implantation, along the length of the stent, or an activity of about 25 microCuries per centimeter of stent length. Ideal dosing for a particular clinical environment can be determined through routine experimentation by those of skill in the art, and may in certain applications fall outside of the foregoing ranges. Advantageously, the isotope attachment of the present invention permits the present invention to

accommodate any of a wide range of desired dosing capabilities as will be appreciated by those of skill in the art in view of the disclosure herein.

Activity and lifetime of sources can be manipulated by the choice of isotope. The relatively rapid time of decay and concomitant loss of "strength" of short half-life isotopes may present product problems in addition to manufacturing problems. Because the isotope is contained on an implanted substrate and has a short half-life, a lack of consistent dosing may result. Take for example, P-32 implanted on three stents at the same time to a level of 10 μCi using the method described in the above-cited paper by Hehrlein (Circulation, 1996). Assume all stents are prepared and available for implantation on day 0. If the first stent is implanted immediately, the second after 7.1 days (one half of a half-life), and the third after 14.3 days (one half-life), then the total dose delivered by the second and third stents, as compared to the first stent, is 29% less for the second stent and 50% less for the third stent. It should be pointed out that the standard of practice for allowable variation in administered dose is 10%.

The radioisotopes used in the radiation delivery sources of the present invention may be beta or gamma emitters, or both, and may have any of a wide range of half-lives, both long and short. The particular isotope, as well as the concentration of the isotope in the source which determines the dose, can be chosen by one skilled in the art to serve the needs of a particular application. In a recent paper presented by Howard Amols at the January 1998 Scripps Clinic Conference on Intravascular Radiation Therapy entitled "Choosing the Right Isotope: What's New? Insights into Isotopes or Why Is it so Hard to Find the Ideal Isotope?," the author states that the best isotope choice from the perspective of both physics and dosimetry would be a photon source with an energy greater than 3 MeV and a half-life greater than 7 days. Shirish K. Jani, in a lecture entitled "Does the Perfect Isotope Exist?" at the same conference states that the perfect isotope for vascular brachytherapy would exhibit a low dose gradient, low dose levels to surrounding body tissues, manageable radiation exposure levels around the patient and a long half-life. Iodine-125 (I-125, half-life 60 days) and tungsten-188/rhenium-188 (W/Re-188, half-life 70 days) are candidates to meet these criteria, and also have long half-lives, and thus are two especially preferred radioisotopes for use in the present invention. Preferred radioisotopes used in the radiation delivery sources of the present invention may be purchased from Oak Ridge National Laboratory (Oak Ridge, TN), New England Nuclear (NEN) or any other commercial suppliers of radioisotopes.

Preferred methods of making the isotope layer of the present invention may begin with either a substrate to be coated directly or a tie layer to which the isotope layer is to be bound. Preferred methods comprise exposing surfaces to fluids comprising reactants or isotopes. Such fluids may be gaseous (including plasma or vapor) or liquid (such as solutions), with liquid solutions being preferred. As such, the methods below are described in terms of liquid solutions.

Preferred methods of making the isotope layer of the radiation delivery sources of the present invention comprise, in part, either one or both of the following solution processes: (1) oxidation in an acidic solution to form a metal salt from a metal; and (2) ion exchange wherein ions at or near the surface of the metal salt are exchanged with those present in a solution. The first process is based on differences in oxidation-reduction potentials, and the second process is based on differences in solubility. These processes will be taken in turn.

In the first process, the equilibrium is driven by principles of oxidation-reduction (redox). A metal, in the form of a pure metal or part of an alloy, may be converted to a metal salt when it is placed in solution comprising an oxidizing agent. Many metals, including those in preferred embodiments discussed below, can be readily oxidized in solution to form metal cations, which may then form salts with anions in solution.

Whether or not a particular reaction of an oxidizing agent and a metal will occur spontaneously can be predicted by reference to a standard table of half-cell potentials such as that in CRC Handbook of Chemistry and Physics, (CRC Press). If the sum of the potentials of the oxidation half-reaction and the reduction half-reaction is positive, then the reaction will occur spontaneously.

For example, it can be predicted that when silver is added to an acid solution of sodium chlorite, the silver will be oxidized. When added to the solution, sodium chlorite ($NaClO_2$) disproportionates to form hypochlorous acid and chlorine dioxide, which is capable of oxidizing silver as shown below:

$$Ag \longrightarrow Ag^+ + e^- \ (ox) \qquad Emf = -0.80\ V$$

$$ClO_2 + e^- \longrightarrow ClO_2 \ (red) \qquad Emf = 1.16\ V$$

$$Ag + ClO_2 + e^- \longrightarrow Ag^+ + ClO_2 \qquad Emf = 0.36\ V$$

In addition to the reaction shown above, the hypochlorous acid undergoes a redox reaction whereby chloride ions are produced which then couple with the silver cations to form silver chloride.

The second process is a solubility-driven ion exchange. When, for example, two anions are placed in solution with a given cation, there is a driving force which results in the formation of the metal salt which is less soluble/more insoluble. Because it is difficult to compare solubilities and thus predict behavior when the relative terms "soluble" and "insoluble" are used, solubility is related to a type of equilibrium constant, the solubility product or K_{sp}, in order to quantify the degree of solubility for a given compound. The solubility product is equal to the concentrations of the dissociated ions of the salt at equilibrium, that is for salt AB, $K_{sp} = [A^+][B^-]$ wherein $[A^+]$ and $[B^-]$ are the concentrations of the A cation and the B anion, respectively. If a salt is fairly soluble, the concentrations of its component ions in solution will be relatively high, leading to a relatively large K_{sp}. On the other hand, if a salt is fairly insoluble, most of it will be in solid form, leading to low concentrations of the ions and a relatively small K_{sp}. Thus, when comparing two salts of the same metal, the salt with the lower K_{sp} is the more insoluble of the two. Solubility products for most common compounds can be found in reference texts such as the CRC Handbook of Chemistry and Physics (CRC Press).

The salts silver chloride (AgCl, $K_{sp} = 1.77 \times 10^{-10}$) and silver iodide (AgI, $K_{sp} = 8.51 \times 10^{-17}$) can be used to illustrate the principle of solubility driven ion exchange. The solubility products for these compounds are both fairly low, but K_{sp} for silver iodide is lower by nearly 7 powers of ten, indicating that it is more insoluble than silver chloride. Thus, if solid silver chloride is placed in a solution containing iodide ions, the equilibrium lies on the side of the silver iodide, and the chloride ions will exchange with the iodide ions so that the more insoluble silver iodide is formed. On the other hand, if silver iodide is placed into a solution containing chloride ions, the ion exchange will not take place. In this manner, chloride ions in silver chloride coated on the surface of a substrate can be replaced by ^{125}I anions to form a radiation source of the present invention.

The metal salt layer which is the starting point for the above solution ion exchange process may be formed by a redox process such as that described above, or it may be applied directly by means of sputtering, vapor deposition, or other techniques known in the art.

Alternatively, if a redox process described above is performed using an oxidizing solution containing a radioisotope, for example $H_3{}^{32}PO_4$, the radioisotope-containing metal salt layer may be obtained directly, eliminating the need for the ion exchange.

Another preferred method for making radiation-delivery stents of the present invention comprises oxidizing a metal, such as those bound to or incorporated in the stent substrate, and then binding an isotope to the metal oxide. The step in which the metal is oxidized preferably occurs spontaneously in air. Thus, metals such as aluminum and copper, which readily and spontaneously undergo oxidation to form their respective oxides, are preferred. Oxide formation occurs when the metal is exposed to air, but may be enhanced or increased by exposure to oxygen-enriched atmospheres or increased temperature. The binding of the isotope is preferably performed by immersing the metal oxide in a solution containing isotope ions, either simple or complex. The attraction between the metal oxide and the isotope ions is such that the isotope ions will bind to the metal oxide rather than existing free in solution. This binding or "plating" process may occur either with or without displacement of ions from the metal oxide.

There are several advantages to using the processes above to place active isotopes on a stent as opposed to the conventional techniques of ion implantation of radioisotopes and nuclear bombardment. One advantage is that unwanted isotopes are not formed. As discussed above with reference to Hehrlein '177, neutron activation of a stent produces numerous isotopes which makes it very difficult to control the dose provided by the stent.

Another advantage of the present method is that it does not create large quantities of radioactive waste. By using the correct quantity of radioisotope solution, very little waste is produced. Isotopes which are not incorporated into a given source remain in solution and may be used on another source. Unlike radioactive ion implantation, there is no machine chamber filled with stray isotopes which must be cleaned and safely discarded.

Another advantage of the present invention is that the production process lends itself to batch processing. The attachment of metal layers, such as those which act as tie layers or to which isotopes are later bound, can be done in very large volumes using common chemical attachment techniques found in the semiconductor, solar energy, and packaging industries such as vapor deposition, electrodeposition, ion plating, ion implantation and sputtering. The radioisotopes are most commonly provided in solutions, so the isotope ion exchange or plating step is as simple as soaking the metal salt or metal oxide coated substrate in a solution of isotope. This step can be done in either very small or very large batch sizes, allowing the amount of radiation in the process to be limited accordingly.

Yet another advantage of the present method is that it allows use of isotopes which cannot be readily obtained on a solid source by the other means known in the art. With the proper choice of materials and solutions and the disclosure herein, one skilled in the art would be able to create a reaction scheme to make a salt containing the most of the desirable therapeutic radioisotopes. Furthermore, by using particular long-lived isotopes a radiation source with a longer half-life can be produced,

which is capable of delivering a dose with less variation between maximum and minimum. Use of an isotope with a longer half-life may provide for a radiation source which is capable of lowering the amount of radioactivity necessary to perform its function over that which incorporates a short-lived isotope.

Another advantage of the present invention is that the radioisotopes are held by strong atomic-level bonding interactions, and which are highly resistant to leaching or release under physiological conditions. Additionally, the use of ionic bonding is especially useful for radioisotope species such as iodine-125, as the salt form holds the normally volatile iodine atoms in place.

Another benefit to the solution processes of the present invention is that the density of activity of a given isotope or multiple isotopes may be controlled by simply controlling the time of immersion and/or the density and amount of metal salt or tie layer on the stent.

The basic method, as discussed in part above, comprises providing a stent and forming a coating comprising an insoluble metal salt with at least one radioactive isotope species thereon.

One preferred embodiment of radiation delivery source of the present invention is that which has an isotope layer comprising the gamma-emitting isotope ^{125}I. As mentioned previously, ^{125}I meets the criteria of an "ideal" isotope as defined by Amols and Jani. One method for making a radiation delivery source having an isotope layer comprising ^{125}I is that which uses both solution methods discussed above. First, a stent is provided with silver in the metal alloy or elemental silver is attached to the surface of the stent using well-known methods such as ion implantation, vapor deposition, sputtering, electroplating, or rolling. The silver is then converted to silver chloride (AgCl) via an oxidation-reduction solution process such as that described above, which uses an acidic solution of sodium chlorite to reduce the silver and produce silver chloride. Then the silver chloride coated stent is immersed into an ion exchange solution of sodium iodide in the form of $Na^{125}I$, wherein the AgCl is converted to $Ag^{125}I$ on the surface of the stent. This manufacturing process may be performed quickly, easily and efficiently. In addition, the I-125 with a half-life of 60 days would provide an equivalent or lower dose of radiotherapy for a longer period of time.

As an alternative to the above method, silver chloride could be directly deposited to the stent surface by means of vapor deposition or other method known in the art, and then immersed in the ion exchange solution containing $Na^{125}I$.

In an experiment done to demonstrate activity which may be achieved by methods of the present invention, Silver foil having a surface area of 4 cm^2 was immersed in a solution of 6M HCl and 1M $NaClO_2$ in a 10:1 ratio. A portion of the silver was converted to silver chloride. The foil was then immersed in a bath having about 2 ml of solution. The solution in the bath had about 0.07% $Na^{125}I$ in NaI, and was prepared by dissolving 0.5 mg NaI in 2ml water and adding 4.6 mCi ^{125}I into solution. Following immersion, the resulting activity of the foil was measured at 2mCi, which, when the amount of carrier (non-radioactive) iodine is factored in, corresponds to about 10^{18} atoms of iodine attached to the sheet. In a carrier free solution, this number of I-125 ions would result in an activity of 3Ci per 4cm^2 of substrate. This is 30,000 times the required activity for a 10 μCi stent.

Another preferred embodiment of radiation delivery source of the present invention is that which has an isotope layer comprising ^{32}P. A radiation delivery source having an isotope layer comprising ^{32}P can be made by methods similar to that

described above for ^{125}I using P-32 in the form of orthophosphoric acid ($H_3{}^{32}PO_4$) (New England Nuclear). First, a stent is provided. The stent may be manufactured to contain zinc or a zinc alloy, or it may be coated with zinc or a zinc alloy by vapor deposition or other methods known in the art. The zinc may then be converted to a relatively insoluble salt such as zinc fluoride (ZnF_2, K_{sp} = 3.04 x 10^{-2}) via an oxidation-reduction process similar to that discussed above. The source is then activated by immersing the zinc fluoride coated stent in a solution containing phosphate ion in the form of $^{32}PO_4^{3-}$ or a soluble phosphate salt, whereby the more soluble fluoride ion is exchanged for phosphate to form zinc phosphate ($Zn_3(PO_4)_2$, K_{sp} = $5x10^{-36}$).

Alternatively, the stent may be directly coated with zinc fluoride or other similarly insoluble salt by vapor deposition or other means known in the art, and then placed in an ion exchange solution. Another alternative is to use an oxidizing solution containing $H_3{}^{32}PO_4$ so that the zinc is directly converted to zinc phosphate containing the radioisotope, thus eliminating the ion-exchange step. Yet another alternative is to deposit or form calcium fluoride (CaF_2, K_{sp} = $1.61x10^{-10}$) and then expose this to a source of phosphate such as $H_3{}^{32}PO_4$ or $Na_3{}^{32}PO_4$.

There is an additional advantage to using $Zn_3(^{32}PO_4)_2$ in the isotope layer. Zinc phosphate is a stable molecule and is often used in the automotive industry for paint adhesion to galvanized steel. Zinc phosphate has anticorrosive characteristics of its own, and has been used in the past to increase the corrosion resistance of steel. A zinc phosphate coating on a steel stent may be an advantage to the stent even in the case that it is not used as a radiation delivery device.

Yet another preferred embodiment of radiation delivery source of the present invention is that which has an isotope layer comprising tungsten-188 (W-188 or ^{188}W). Tungsten-188 undergoes beta decay to become rhenium-188 (Re-188 or ^{188}Re). Rhenium-188 undergoes beta decay as well, but emits a much higher energy particle than in W-188 decay. The W-188 has a much longer half-life than does Re-188, thus the W-188 almost continuously creates more Re-188. This process is known as "generator," and the generator isotopes are referred to together by the shorthand W/Re-188 to indicate the relationship between the species. Generators are attractive for use in radiation delivery devices because they combine the energy levels of a short half-life species with the durability of the long half-life species. It is a general rule that particle energy and half-life are inversely proportional, and that long half-life species are more economical and practical to work with than short half-life species.

W/Re-188 is a beta emitting isotope with an energy about 10% higher than P-32. Where I-125 was discussed as a perfect gamma emitting isotope, W/Re-188 fits the criteria of both Amols and Jani for a perfect beta emitting species for IVRT. The advantage of the W/Re-188 stent would be that the dose would be consistently administered over a long period of time. The half-life of W-188 is 70 days as compared to 14 days for the P-32. This represents a consistent dose rate as Re-188, itself a beta emitting isotope, is being produced by the decay of tungsten for a longer period of time.

Tungsten, in the form of tungstate ion (WO_4^{2-}) may be readily attached to an oxidized aluminum surface to produce a W/Re-188-containing radiation delivery source of the present invention. An aluminum oxide surface may be attached to the stent by sputtering Al_2O_3, or Al can be attached by implantation or deposition, followed by an oxidation step. Ambient environment will facilitate the formation of Al_2O_3 from aluminum which can be accelerated by increasing the temperature and/or using an oxygen-rich atmosphere. The aluminum oxide surface may then be immersed in a tungstate containing solution, such as an acidic solution of sodium tungstate ($Na_2{}^{188}WO_4$), in order to attach the W-188 to the alumina surface.

Tungsten may also be applied together with a phosphate in a manner similar to that disclosed by Larsen in U.S. Patent No. 5,550,006, which is hereby incorporated into the present disclosure by this reference thereto. The method disclosed in Larsen is claimed for use in increasing adhesion of organic resists for printed circuits. The method was used to perform a phosphate conversion coating onto copper. This method may find its application in the radiation delivery device of the present invention in that many polymers and metals other than copper may be coated with this solution. In this method, phosphate may be in the form of $^{32}PO_4^{3-}$, tungstate may be in the form of $^{188}WO_4^{2-}$, or any combination of the isotopes in radioactive or stable form may be used.

Combinations of various isotopes provide another preferred embodiment in that beta-emitting isotopes may be combined with gamma-emitting isotopes where gamma isotopes can deliver dosage to greater depths.

Radiation delivery sources comprising other metals, metal salts, and isotopes can be made by procedures similar or analogous to the preferred embodiments disclosed above, using materials appropriate for the chemistry of the isotope to be included, as can be determined by one skilled in the art in view of the disclosure herein.

In some embodiments of the radiation delivery source of the present invention, it may be desirable to provide a tie layer, onto which the isotope layer can be placed. The tie layer may comprise adhesives, chemically activated surfaces, a chemical coating layer, or an organic or inorganic compound. Preferably the tie layer is a layer of metal, metal oxide, metal salt or alloy. Depositing a metal-type layer may allow an alloying process to take place, which will enhance the tenacity of attachment of the metal salt, and hence the isotope species. This is common in the semiconductor industry, wherein a chromium layer is used as an initial layer in the deposition of gold. The chromium is alloyed with the gold in order to increase the strength at which the gold is bound to the substrate. If, for example, the isotope layer comprises a zinc salt, a metal such as copper or aluminum may be used as the tie layer. The tie layer may also be in the form of an oxide that provides oxygen to chemically bind the atoms of the metal salt layer thereby increasing the tenacity of attachment.

The first metal layer to which the isotope layer is attached may comprise any suitable metal or metal oxide. The layer may be deposited by vapor deposition, sputtering, ion plating, ion implantation, electrodeposition, or other method. When the tie layer is present, there may or may not be a clear distinction between the tie layer and the isotope layer. In performing its function, and depending on the chemistry of the materials involved, the tie layer may become blended, alloyed or intermingled with the isotope layer, thus blurring the lines between the layers. For many of the same reasons, the distinction between the tie layer and a metal-containing substrate layer may also be blurred. In these cases, the term tie layer is meant to be a functional or process-defining definition, rather than a reference to a physically distinct layer of the radiation delivery source.

Although the stents of the present invention may have isotopes which are sufficiently adherent without further treatment, in some embodiments of the present invention, it may be desirable to place an outer coating on the radiation delivery source. An outer coating can provide further advantages for the radiation delivery source of the present invention in that the coating can help provide additional means to bind the layers of the source together. Perhaps more importantly, an outer coating can increase the abrasion resistance of the source.

Sealed radioactive sources are those which have less than 5 nCi of removable activity. By providing a coating on the source which covers at least the isotope layer, the source can be protected from unwanted loss of activity due to mechanical abrasion of the surface of the source. This may be important, both for providing safe devices for the patient which leave radioisotopes behind only where they are desired, and for monitoring dosage to ensure that the dose which is to be provided by a source will actually reach the treatment site, and not be significantly diminished due to loss of isotope from abrasion which may occur during implantation. It also helps insure that, once the source is positioned, the radioisotopes will remain at the placement site and not be washed downstream.

Coating materials are preferably biocompatible, but not excessively biodegradable. Preferred materials include cyanoacrylates (Loctite, Hartford, CT), acrylics, ethylene methyl acrylate (Exxon Chemical Co., Houston, TX), ethylene methyl acrylate/acrylic acid (EMA/AA) (Exxon Chemical Co., Houston, TX), urethanes and thermal plastic urethane (TPU) (BF Goodrich, Richfield, OH), PVDC (Saran, Dow Chemical, Midland, MI), PBVC, PE, PET, and the like. Other preferred coatings may comprise other biocompatible materials, drugs or similar compounds, such as heparin. Many methods are available to perform the coating process, such as dip or immersion coating, spray coating, spin coating, and gravure. If a material requires curing, the curing technique may be any of the various techniques available, such as air, heat, or UV. Preferably the thickness of the coating which is formed is 1μm to 30μm more preferably 10μm to 20μm.

One preferred embodiment of the present invention has a coating that is formed with cyanoacrylate. Another preferred coating layer is that formed by ethylene methyl acrylate/acrylic acid (EMA/AA). An aqueous dispersion of this coating material, preferably having a viscosity less than 100 centipoise, allows for use of any of the above-mentioned coating methods. UV curable polyurethane acrylate is also useful as a coating layer material. Yet another preferred coating layer is that formed by SARAN. Such a layer may be formed, for example, by immersing the source or a portion thereof into a melt of SARAN or a solution containing SARAN.

The coating layer may also be formed by a spin coating process. Spin coating the thin film source finds advantage in the flexibility to use coating materials having a wide range of viscosities. Low viscosity liquids may be spun on slowly, while a higher viscosity liquid may be spun at a higher velocity to maintain a thin coating. The substrate may be held in place by fixturing or by vacuum during the spin coating process. In an experiment, a dispersion of cyanoacrylate in acetone was dispensed on top of the metal salt surface while the substrate was rotated at 8000 rpm for five minutes. The resulting thickness of the coating was about 6.5μm (0.00025 inch). When this specimen, having the spin-coated surface curable coating of cyanoacrylate was extracted in saline for 8 hours at 50°C, the amount of radioactivity extracted was negligible.

Implantation of the radiation delivery source of the present invention may be done according to methods for implanting stents, as are known in the art. For example, if the stent which forms the substrate of a radiation delivery source of the present invention is of the self-expanding variety, the following technique may be used for implantation in a body lumen, such as a coronary artery. Initially the source is compressed into a first shape and then restrained such as by placement within a hollow recess at the distal end of a catheter. The catheter is then inserted percutaneously and advanced through the vasculature of the patient until the treatment site such as within the coronary artery is reached. A pusher is then advanced through the lumen

of the catheter in which the source resides, and made to push on the proximal end of the source so that it is forced out the distal end of the catheter into the artery of the patient. Proximal retraction of an outer restraining sheath may also be utilized to release a self expandable stent as will be understood by those of skill in the art. Once freed from the catheter, the source expands into contact with the wall of the artery.

If the stent used for the substrate of the radiation delivery source is of the variety which does not self-expand, the following technique as is known in the art may be used to implant the source into a body lumen, such as a coronary artery. This technique relies on the use of an expansion catheter such as a balloon catheter. The balloon catheter may be used simply as a delivery device, or it may be used to provide simultaneous dilatation of a stenosis and implantation of the source. The source is first positioned on the balloon prior to percutaneous insertion within the patient. The balloon carrying a stent thereon is thereafter percutaneously inserted and transluminally advanced through the patient's vasculature to the treatment site. If desired, the balloon and source may be introduced through an introduction sheath, which can be proximally withdrawn to expose the source and balloon once they have been positioned at the treatment site. The balloon is then expanded at the treatment site to expand the stent. The balloon is thereafter deflated, and withdrawn from the patient, leaving the expanded stent in position at the site.

In accordance with another aspect of the present invention, there is provided a method of treating a site within a vessel. This method proceeds by first identifying a site within a vessel to be treated, and then providing a radiation delivery source in the form of a stent, as described elsewhere herein. Finally, the source is placed at the treatment site by a technique such as that described above, and left in place to deliver its dose of radiation to the treatment site.

Although the present invention has been described in terms of certain preferred embodiments, other embodiments of the invention will become apparent to those of skill in the art in view of the disclosure herein. Accordingly, the scope of the present invention is not intended to be limited by the foregoing, but rather by reference to the attached claims.

WHAT IS CLAIMED IS:

1. A radiation delivery source in the form of a stent, comprising:

a substrate in the form of a stent; and

an isotope layer on the substrate, wherein said isotope layer comprises a metal salt or oxide, and at least one isotope.

2. The radiation delivery source of Claim 1, wherein said isotope is a gamma emitting isotope or a beta emitting isotope.

3. The radiation delivery source of Claim 1, wherein said isotope is selected from the group consisting of P-32, I-125, W/Re-188, Pd-103, Gd-153, As-73, and combinations thereof.

4. The radiation delivery source of Claim 1, further comprising a coating layer.

5. The radiation delivery source of Claim 4, wherein said coating layer comprises a material selected from the group consisting of cyanoacrylates, acrylics, acrylates, ethylene methylacrylate/acrylic acid, urethanes, polybutyl vinyl chloride, polyvinylidene chloride, and other polymeric materials.

6. The radiation delivery source of Claim 4, wherein said coating layer comprises a biocompatible substance.

7. A radiation delivery source in the form of a stent, comprising:

a substrate in the form of a stent;

a tie layer; and

an isotope layer on the tie layer, wherein said isotope layer comprises a metal salt or oxide, and at least one isotope;

wherein said tie layer lies between said substrate and said isotope layer.

8. The radiation delivery source of Claim 7, wherein said isotope is a gamma emitting isotope or a beta emitting isotope.

9. The radiation delivery source of Claim 7, wherein said isotope is selected from the group consisting of P-32, I-125, W/Re-188, Pd-103, As-73, Gd-153, and combinations thereof.

10. The radiation delivery source of Claim 7, wherein said tie layer comprises a material selected from the group consisting of a metal, metal oxide, metal salt and alloy.

11. The radiation delivery source of Claim 7, further comprising a coating layer.

12. The radiation delivery source of Claim 11, wherein said coating layer comprises a material selected from the group consisting of cyanoacrylates, acrylics, acrylates, ethylene methylacrylate/acrylic acid, urethanes, polybutyl vinyl chloride, polyvinylidene chloride, and other polymeric materials.

13. The radiation delivery source of Claim 11, wherein said coating layer comprises a biocompatible substance.

14. A method for making a radiation delivery source in the form of a stent, comprising the steps of:

providing substrate in the form of a stent;

coating at least one surface of said substrate with a isotope layer comprising a metal salt or oxide, and at least one isotope.

15. The method of Claim 14, wherein said isotope is a gamma emitting isotope or a beta emitting isotope.

16. The method of Claim 14, wherein said isotope is selected from the group consisting of P-32, I-125, W/Re-188, Pd-103, As-73, Gd-153, and combinations thereof.

17. The method of Claim 14, wherein said coating step comprises the steps of:

coating said substrate with at least one layer of metal;

reacting said layer of metal to form a layer of metal oxide or metal salt; and

exposing said layer of metal oxide or metal salt to a fluid comprising a plurality of radioisotope ions to form said isotope layer.

18. The method of Claim 17, wherein the fluid is a solution.

19. The method of Claim 14, wherein said coating step comprises the steps of:

coating said substrate with a layer of metal salt or metal oxide; and

exposing said layer of metal oxide or metal salt to a fluid comprising a plurality of radioisotope ions to form said isotope layer.

20. The method of Claim 19, wherein the fluid is a solution.

21. The method of Claim 14, further comprising the step of coating said isotope layer with a coating layer.

22. The method of Claim 21, wherein said coating layer comprises a material selected from the group consisting of cyanoacrylates, acrylics, acrylates, ethylene methylacrylate/acrylic acid, urethanes, polybutyl vinyl chloride, polyvinylidene chloride, and other polymeric materials.

FIG. 1

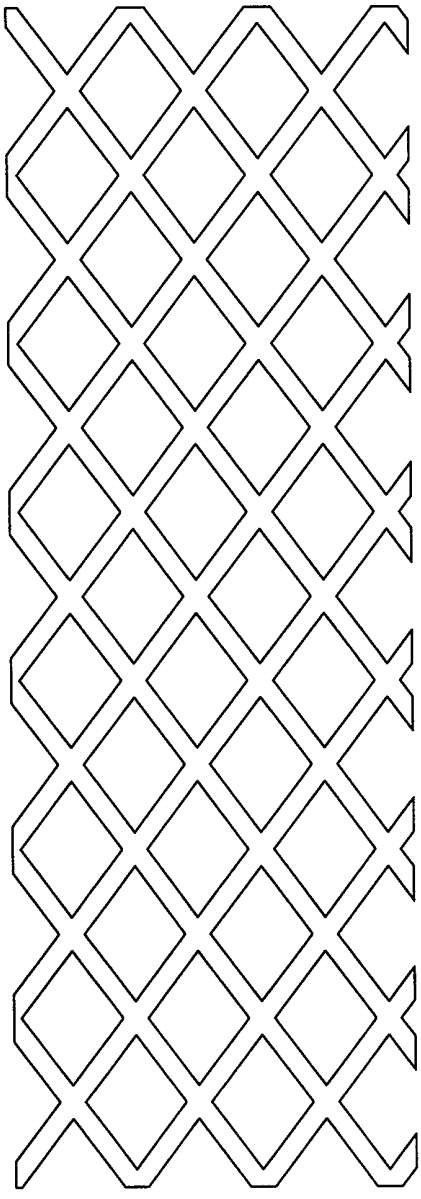


FIG. 2a

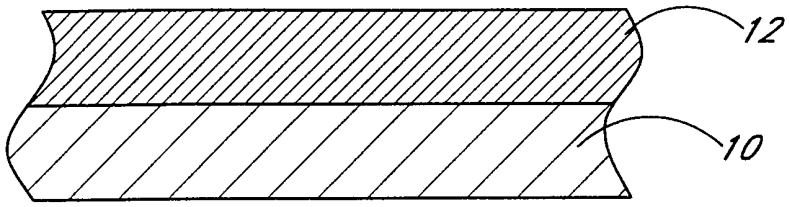


FIG. 2b

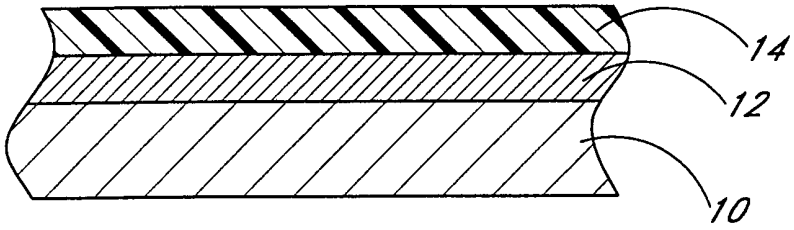


FIG. 2c

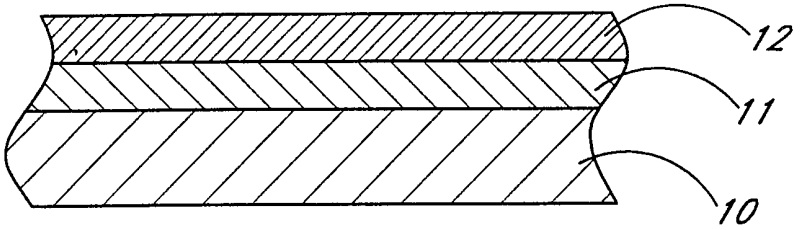


FIG. 2d

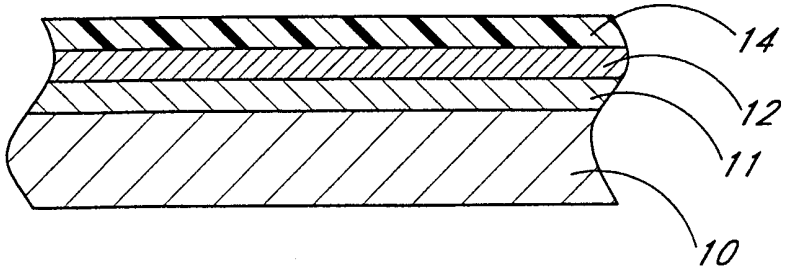


FIG. 3a

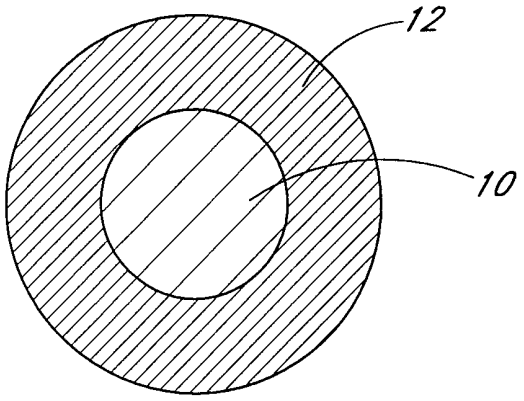


FIG. 3b

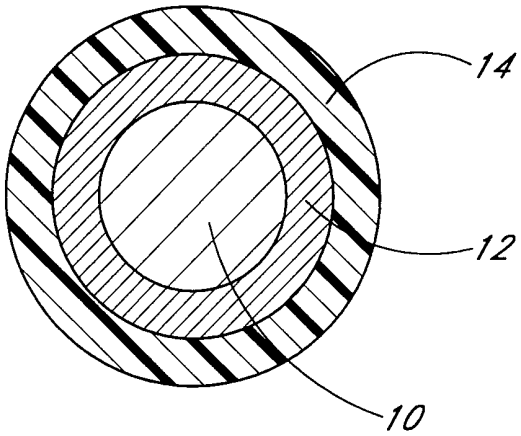


FIG. 3c

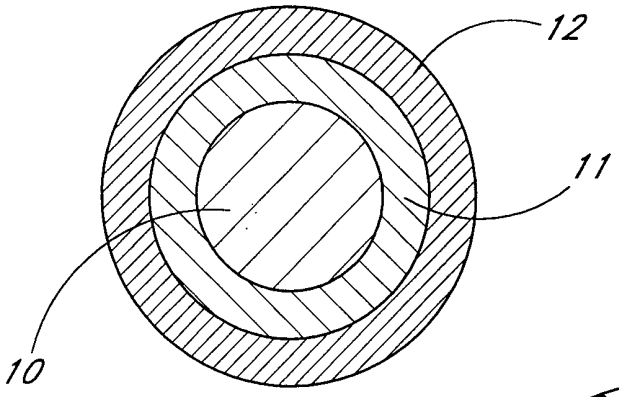
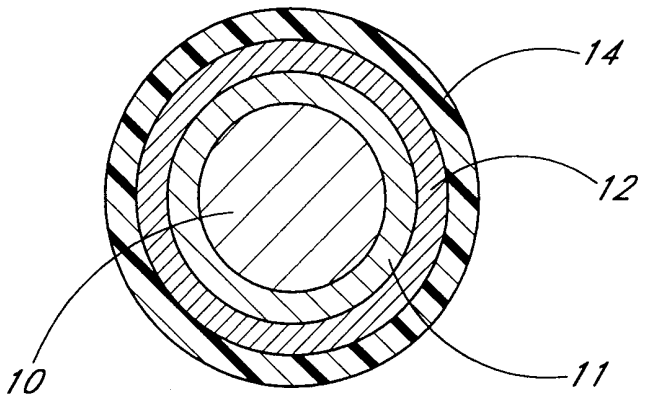


FIG. 3d



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/03600

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61N 5/00
US CL :600/003

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 29/592; 264/0.5; 600/001-008

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,059,166 A (FISCHELL ET AL) 22 October 1991, entire document.	1-22
Y	US 5,176,617 A (FISCHELL et al) 05 January 1993, entire document.	1-22
Y	US 5,411,466 A (HESS) 02 May 1995, entire document.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 21 APRIL 1999	Date of mailing of the international search report 12 MAY 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SAMUEL GILBERT Telephone No. (703) 308-3553

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