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(54) Title: BIOERODIBLE ENDOPROSTHESES AND METHODS OF MAKING THE SAME

(57) Abstract: The invention relates to bioerodible endoprostheses and methods of making the endoprostheses. The endoprostheses can be configured to erode in a controlled and predetermined manner in the body. In one aspect, the invention features an endoprosthesis that includes a first metallic portion having a first erosion rate, and a second metallic portion having a second erosion rate different from the first erosion rate.

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BIOERODIBLE ENDOPROSTHESES AND METHODS OF MAKING THE SAME

TECHNICAL FIELD

The invention relates to bioerodible endoprostheses, and to methods of making the same.

BACKGROUND

The body includes various passageways such as arteries, other blood vessels, and other body lumens. These passageways sometimes become occluded or weakened. For example, the passageways can be occluded by a tumor, restricted by plaque, or weakened by an aneurysm. When this occurs, the passageway can be reopened or reinforced with a medical endoprosthesis. An endoprosthesis is typically a tubular member that is placed in a lumen in the body. Examples of endoprostheses include stents, covered stents, and stent-grafts.

Endoprostheses can be delivered inside the body by a catheter that supports the endoprosthesis in a compacted or reduced-size form as the endoprosthesis is transported to a desired site. Upon reaching the site, the endoprosthesis is expanded, e.g., so that it can contact the walls of the lumen.

The expansion mechanism may include forcing the endoprosthesis to expand radially. For example, the expansion mechanism can include the catheter carrying a balloon, which carries a balloon-expandable endoprosthesis. The balloon can be inflated to deform and to fix the expanded endoprosthesis at a predetermined position in contact with the lumen wall. The balloon can then be deflated, and the catheter withdrawn from the lumen.

It is sometimes desirable for an implanted endoprosthesis to erode over time within the passageway. For example, a fully erodible endoprosthesis does not remain as a permanent object in the body, which may help the passageway recover to its natural condition. Erodible endoprostheses can be formed from, e.g., a polymeric material, such as polylactic acid, or from a metallic material, such as magnesium, iron or an alloy thereof.

SUMMARY

The invention relates to bioerodible endoprostheses and methods of making the endoprostheses. The endoprostheses can be configured to erode in a controlled and predetermined manner in the body.

In one aspect, the invention features an endoprosthesis that includes a first metallic portion having a first erosion rate, and a second metallic portion having a second erosion rate different from the first erosion rate.

The first and second metallic portions can, e.g., include a common metal, e.g., magnesium, calcium, zinc or iron. In some instances, at least one of the metallic portions is substantially a pure metal. In some embodiments, the first metallic portion includes an outside surface or an inside surface of the endoprosthesis, and the second metallic portion is disposed inwardly of the first portion. The first and second metallic portions can be, e.g., circular in a transverse cross-section. One of the metallic portions can be, e.g., formed from a metallic alloy.

In some embodiments, a thickness of the metallic portion having a lower erosion rate is from about 10 nm to about 1000 nm, e.g., from about 15 nm to about 100 nm.

The erosion rate of the metallic portion having a lower erosion rate can be, e.g., from about 0.01 percent of an initial mass of that portion per day to about 1 percent of the initial mass of that portion per day, e.g., from about 0.1 percent of the initial mass of that portion per day to about 0.5 percent of the initial mass of that portion per day.

The erosion rate of the metallic portion having a higher erosion rate can be, e.g., from about 0.2 percent of an initial mass of that portion per day to about 10 percent of the initial mass of that portion per day, e.g., from about 0.5 percent of the initial mass of that portion per day to about 5 percent of the initial mass of that portion per day.

The erosion rate of the metallic portion having the higher erosion rate can be, e.g., from about ten percent to about one-hundred percent greater than the erosion rate of the metallic portion having the lower erosion rate.

In some embodiments, the first and second metallic portions are disposed within a longitudinal segment of the endoprosthesis. The endoprosthesis can

include a plurality of segments, e.g., arranged along a longitudinal length of the endoprosthesis.

In some embodiments, the endoprosthesis is adapted to erode sequentially along a longitudinal length of the endoprosthesis, e.g., in a direction transverse to the longitudinal length of the endoprosthesis.

In some embodiments, the endoprosthesis includes an inner surface, an outer surface, and a portion between the inner and outer surfaces. The portion between the inner and outer surfaces has an erosion rate higher than an erosion rate of the inner surface or the outer surface.

In some embodiments, the endoprosthesis is tubular in form.

The endoprosthesis can, e.g., include a stent.

In another aspect, the invention features a method of making an endoprosthesis that includes implanting a material into a first portion of an erodible endoprosthesis. The implanted first portion has a higher concentration of the first material than a second portion of the endoprosthesis. In some embodiments, the first portion has a different erosion rate than the second portion. The implanted material can include, e.g., nitrogen, carbon, silicon, oxygen, sulfur, chromium, silver, gold, boron, or mixtures of these elements. The erodible endoprosthesis can include, e.g., magnesium, calcium, lithium, rare earth elements, iron, aluminum, zinc, manganese, cobalt, copper, zirconium, titanium, or mixtures of these elements.

In some embodiments, the implanting employs a plasma.

In some embodiments, the method further includes, prior to implanting, applying a shielding, e.g., a coating, e.g., a polymeric coating, to a portion of the endoprosthesis. In some embodiments, after applying the shielding, the method further includes removing the applied shielding.

Aspects and/or embodiments may have one or more of the following advantages. The endoprostheses may not need to be removed from a lumen after implantation. The endoprostheses can have a low thrombogenecity and high initial strength. The endoprostheses can exhibit reduced spring back (recoil) after expansion. Lumens implanted with the endoprostheses can exhibit reduced restenosis. The rate of erosion of different portions of the endoprostheses can be controlled, allowing the endoprostheses to erode in a predetermined manner,

reducing, e.g., the likelihood of uncontrolled fragmentation. For example, the predetermined manner of erosion can be from an inside of the endoprosthesis to an outside of the endoprosthesis, or from a first end of the endoprosthesis to a second end of the endoprosthesis.

An erodible or bioerodible endoprosthesis, e.g., a stent, refers to an endoprosthesis, or a portion thereof, that exhibits substantial mass or density reduction or chemical transformation, after it is introduced into a patient, e.g., a human patient. Mass reduction can occur by, e.g., dissolution of the material that forms the endoprosthesis and/or fragmenting of the endoprosthesis. Chemical transformation can include oxidation/reduction, hydrolysis, substitution, and/or addition reactions, or other chemical reactions of the material from which the endoprosthesis, or a portion thereof, is made. The erosion can be the result of a chemical and/or biological interaction of the endoprosthesis with the body environment, e.g., the body itself or body fluids, into which it is implanted and/or erosion can be triggered by applying a triggering influence, such as a chemical reactant or energy to the endoprosthesis, e.g., to increase a reaction rate. For example, an endoprosthesis, or a portion thereof, can be formed from an active metal, e.g., Mg or Ca or an alloy thereof, and which can erode by reaction with water, producing the corresponding metal oxide and hydrogen gas (a redox reaction). For example, an endoprosthesis, or a portion thereof, can be formed from an erodible or bioerodible polymer, or an alloy or blend erodible or bioerodible polymers which can erode by hydrolysis with water. The erosion occurs to a desirable extent in a time frame that can provide a therapeutic benefit. For example, in embodiments, the endoprosthesis exhibits substantial mass reduction after a period of time which a function of the endoprosthesis, such as support of the lumen wall or drug delivery is no longer needed or desirable. In particular embodiments, the endoprosthesis exhibits a mass reduction of about 10 percent or more, e.g. about 50 percent or more, after a period of implantation of one day or more, e.g. about 60 days or more, about 180 days or more, about 600 days or more, or 1000 days or less. In embodiments, the endoprosthesis exhibits fragmentation by erosion processes. The fragmentation occurs as, e.g., some regions of the endoprosthesis erode more rapidly than other regions. The faster eroding regions become weakened

by more quickly eroding through the body of the endoprosthesis and fragment from the slower eroding regions. The faster eroding and slower eroding regions may be random or predefined. For example, faster eroding regions may be predefined by treating the regions to enhance chemical reactivity of the regions. Alternatively, regions may be treated to reduce erosion rates, e.g., by using coatings. In embodiments, only portions of the endoprosthesis exhibits erodibilty. For example, an exterior layer or coating may be erodible, while an interior layer or body is non-erodible. In embodiments, the endoprosthesis is formed from an erodible material dispersed within a non-erodible material such that after erosion, the endoprosthesis has increased porosity by erosion of the erodible material.

Erosion rates can be measured with a test endoprosthesis suspended in a stream of Ringer's solution flowing at a rate of 0.2 m/second. During testing, all surfaces of the test endoprosthesis can be exposed to the stream. For the purposes of this disclosure, Ringer's solution is a solution of recently boiled distilled water containing 8.6 gram sodium chloride, 0.3 gram potassium chloride, and 0.33 gram calcium chloride per liter.

As used herein, an "alloy" means a substance composed of two or more metals or of a metal and a nonmetal intimately united, for example, by being fused together and dissolving in each other when molten.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference herein in their entirety.

Other aspects, features, and advantages will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

Fig. 1A is a perspective view of an embodiment of an erodible stent; and Fig. 1B is a cross-sectional view of the stent of Fig. 1A, taken along line 1B-1B.

Figs. 2-4 illustrate erosion of an erodible stent within a body passageway.

Fig. 5 is a schematic cross-sectional view of a plasma immersion ion implantation ("PIII") system.

Fig. 6A is a perspective view of an embodiment of an erodible stent; Fig. 6B is a cross-sectional view of the stent of Fig. 6A, taken along line 6B-6B; and Fig. 6C is a cross-sectional view of the stent of Fig. 6C, taken along line 6C-6C.

Fig. 7 is a perspective view of an embodiment of an erodible stent.

Fig. 8 is a sequence of perspective views illustrating a method of making the stent of Fig. 7.

Fig. 9 is a cross-sectional view of an embodiment of an erodible stent.

Fig. 10 is a cross-sectional view of an embodiment of an erodible stent.

Fig. 11 is a perspective view of an embodiment of an erodible coil stent having a flared end.

Fig. 12 is a perspective view of an embodiment of an erodible coiled stent having a flared end and engaging elements.

Fig. 13 is a perspective view of an embodiment of an erodible wire stent having bands and connectors that extend between and connect adjacent bands.

DETAILED DESCRIPTION

Figs. 1A and 1B show an erodible stent 10 configured to erode in a controlled and predetermined manner. As shown, stent 10 includes a tubular body 13 having an outer portion 20, an inner portion 26, and middle portion 24 between the outer and inner portions. Middle portion 24 has a first metallic composition, such as an erodible magnesium alloy, that has a first erosion rate. Outer and inner portions 20, 26 have a second metallic composition that has a second erosion rate lower than the first erosion rate. For example, the second composition can include the magnesium alloy of middle portion 24 containing magnesium nitride (e.g., Mg_3N_2), which is relatively stable against corrosion and can reduce the erosion rate of the magnesium alloy. Alternatively or additionally, without wishing to be bound by theory, it is believed that the reduction in corrosion can also be due to the densification of the magnesium as a result of nitrogen bombardment (described below). As a result, without changing the bulk mechanical properties of stent 10, outer and inner portions 20, 26 can extend the time it takes the stent to erode to a particular degree of erosion, relative to a stent including the magnesium alloy without the magnesium nitride. This extension of time allows cells of the passageway in which stent 10 is implanted to better endothelialize around the stent, for example, before the stent erodes to a degree where it can no longer structurally maintain the patency of the passageway.

Furthermore, outer and inner portions 20, 26 can be uniform or varied along a direction (e.g., length) of a stent to allow the stent to erode in a predetermined sequence. Figs. 2-4 show a stent 28 implanted in a body vessel 19. Stent 28 is configured to erode progressively from its end portions 14, 16 toward its middle segment 17. For example, outer and inner portions 20, 26 containing magnesium nitride can be relatively thick at middle segment 17 and taper decreasingly in thickness from the middle segment to end portions 14, 16. As a result, end portions 14, 16 can erode before middle segment 17 erodes. This configuration can allow stent 28 to erode in a manner that reduces (e.g., minimizes) the amount of fragments that, if not enveloped by endothelialized cells, may become dislodged and cause complications in the body.

Referring again to Fig. 1B, middle portion 24 of tubular body 13 can include (e.g., be made from) a biocompatible material capable of eroding within the body. The erodible or bioerodible material can be a substantially pure metallic element, or an alloy. Examples of metallic elements include iron and magnesium. Examples of alloys include iron alloys having, by weight, 88-99.8% iron, 0.1-7% chromium, 0-3.5% nickel, and less than 5% of other elements (e.g., magnesium and/or zinc); or 90-96% iron, 3-6% chromium and 0-3% nickel plus 0-5% other metals. Other examples of alloys include magnesium alloys, such as, by weight, 50-98% magnesium, 0-40% lithium, 0-5% iron and less than 5% other metals or rare earths; or 79-97% magnesium, 2-5% aluminum, 0-12% lithium and 1-4% rare earths (such as cerium, lanthanum, neodymium and/or praseodymium); or 85-91% magnesium, 6-12% lithium, 2% aluminum and 1% rare earths; or 86-97% magnesium, 0-8% lithium, 2% -4% aluminum and 1-2% rare earths; or 8.5-9.5% aluminum, 0.15%-0.4% manganese, 0.45-0.9% zinc and the remainder magnesium; or 4.5-5.3% aluminum, 0.28%-0.5% manganese and the remainder magnesium; or 55-65% magnesium, 30-40% lithium and 0-5% other metals and/or rare earths. Magnesium alloys are also available under the names AZ91D, AM50A, and AE42. Other erodible materials are described in Bolz, U.S. 6,287,332 (e.g., zinc-titanium alloy and sodium-magnesium alloys); Heublein, U.S. Patent Application 2002000406; and Park, *Science and Technology of Advanced Materials*, 2, 73-78 (2001), all of which are hereby incorporated by reference

herein in their entirety. In particular, Park describes Mg-X-Ca alloys, e.g., Mg-Al-Si-Ca, Mg-Zn-Ca alloys.

Outer and inner portions 20, 26 of tubular body 13 can include a erodible combination of the erodible material of middle portion 24 and one or more first materials capable of reducing the erosion rate of the erodible material. In some embodiments, the erosion rate of outer and inner portions 20, 26 is from about 10% to about 300% less than the erosion rate of middle portion 24, for example, from about 25% to about 200% less, or from about 50% to about 150% less. The erosion rate of outer and inner portions 20, 26 can range from about 0.01 percent of an initial mass of that portion per day to about 1 percent of the initial mass of that portion per day, e.g., from about 0.1 percent of the initial mass of that portion per day to about 0.5 percent of the initial mass of that portion per day. The erosion rate of middle portion 24 can range from about 0.2 percent of an initial mass of that portion per day to about 10 percent of the initial mass of that portion per day., e.g., from about 0.5 percent of the initial mass of that portion per day to about 5 percent of the initial mass of that portion per day. Examples of first materials include magnesium nitride, magnesium oxide, magnesium fluoride, iron nitride and iron carbide. Iron nitride and iron carbide materials are discussed in Weber, *Materials Science and Engineering,* A199, 205-210 (1995), and magnesium nitride is discussed in Tian, Surface and Coatings Technology, 198, 454-458 (2005), the entire disclosure of each of which is hereby incorporated by reference herein. Outer and inner portions 20, 26 can have the same chemical composition or different compositions. For example, inner portion 26 may contact bodily fluid more than outer portion 20 (which may contact the wall of the body passageway), and as a result, the inner portion may erode more quickly than the outer portion. To compensate for the difference in erosion and to allow a given cross section of stent 28 to erode relatively uniformly from portions 20, 26 to middle portion 24, the inner portion may have a chemical composition that erodes more slowly than the chemical composition of the outer portion.

The concentration(s) of the first material(s) in outer and inner portions 20, 26 can vary, depending on the desired time to erode through the portions. In embodiments in which the first material(s) reduces the erosion rate of the

erodible material, the higher the concentration(s) of the first material(s) in outer and inner portions 20, 26, the more time it takes to erode through the portions. The total concentration of the first material(s) in a portion can range from about 1 percent to about fifty percent. The concentrations of first material(s) in inner portion 26 and outer portion 20 can be the same or different. For example, to compensate for the difference in erosion between portions 20, 26 and to allow a given cross section of stent 28 to erode relatively uniformly from the portions to middle portion 24, the inner portion may have a higher concentration of first material(s) than the outer portion along the cross section.

The thicknesses of outer and inner portions 20, 26 containing the first material(s) can also vary, depending on the desired time to erode through the portions. In embodiments in which the first material(s) reduces the erosion rate of the erodible material, the thicker outer and inner portions 20, 26, the more time it takes to erode through the portions. The thickness of an inner portion or an outer portion including the first material(s) can range from about 1 nm to about 750 nm. The thicknesses of inner portion 26 and outer portion 20 can be the same or different. For example, to compensate for the difference in erosion rates between portions 20, 26 and to allow a cross section of stent 10 to erode relatively uniformly from the portions to middle portion 24, the inner portion may be thicker than the outer portion along the cross section.

The combination of the first material(s) and the erodible material can be formed by plasma treatment, such as plasma immersion ion implantation ("PIII"). During PIII, one or more charged species in a plasma, such as an oxygen and/or a nitrogen plasma, are accelerated at high velocity toward a substrate, such as a stent including the erodible material ("a pre-stent"). Acceleration of the charged species, e.g., particles, of the plasma towards the pre-stent is driven by an electrical potential difference between the plasma and the pre-stent. Alternatively, one could also apply the electrical potential difference between the plasma and an electrode that is underneath the pre-stent such that the stent is in a line-of-sight. Such a configuration can allow part of the pre-stent to be treated, while shielding other parts of the pre-stent. This can allow for treatment of different portions of the pre-stent with different energies and/or ion densities. In some embodiments, the potential difference can be

greater than 10,000 volts, e.g., greater than 20,000 volts, greater than 40,000 volts, greater than 50,000 volts , greater than 60,000 volts, greater than 75,000 volts, or even greater than 100,000 volts. Upon impact with the surfaces of the pre-stent, the charged species, due to their high velocity, penetrate a distance into the pre-stent, react with the erodible material, and form stent 10 having portions 20, 26. The penetration depth is being controlled, at least in part, by the potential difference between the plasma and the pre-stent.

Fig. 5 shows an embodiment of a PIII processing system 80. System 80 includes a vacuum chamber 82 having a vacuum port 84 connected to a vacuum pump and a gas source 130 for delivering a gas, e.g., oxygen or nitrogen, to chamber 82 to generate a plasma. System 80 includes a series of dielectric windows 86, e.g., made of glass or quartz, sealed by o-rings 90 to maintain a vacuum in chamber 82. Removably attached to some of the windows 86 are RF plasma sources 92, each source having a helical antenna 96 located within a grounded shield 98. The windows without attached RF plasma sources are usable, e.g., as viewing ports into chamber 82. Each antenna 96 electrically communicates with an RF generator 100 through a network 102 and a coupling capacitor 104. Each antenna 96 also electrically communicates with a tuning capacitor 106. Each tuning capacitor 106 is controlled by a signal D, D', D" from a controller 110. By adjusting each tuning capacitor 106, the output power from each RF antenna 96 can be adjusted to maintain homogeneity of the generated plasma.

In use, a plasma is generated in chamber 82 and accelerated to a pre-stent 125. Pre-stent 125 can be made, for example, by forming a tube including the erodible material and laser cutting a stent pattern in the tube, or by knitting or weaving a tube from a wire or a filament including the erodible material. A gas, such as oxygen, nitrogen or a silane, is introduced from gas source 130 into chamber 82, where a plasma is generated. The charged species in the generated plasma, e.g., an oxygen or nitrogen plasma, are accelerated toward all portions of pre-stent 125, including exterior 130 and interior portions 132 of the pre-stent, and thus, become implanted in the pre-stent. PIII has been described by Chu, U.S. Patent No. 6,120,260; Brukner , *Surface and Coatings Technology*, 103-

104, 227-230 (1998); and Kutsenko, *Acta Materialia*, 52, 4329-4335 (2004), the entire disclosure of each of which is hereby incorporated by reference herein.

Ion penetration depth and ion concentration can be modified by changing the configuration of the PIII processing system. For example, when the ions have a relatively low energy, e.g., 10,000 volts or less, penetration depth is relatively shallow when compared with the situation when the ions have a relatively high energy, e.g., greater than 40,000 volts. The dose of ions being applied to a surface can range from about 1 X 10^4 ions/cm^2 to about 1 X 10^9 ions/cm^2, e.g., from about 1 X 10^5 ions/cm^2 to about 1 X 10^8 ions/cm^2.

In some embodiments, as indicated above, outer and inner portions 20, 26 can be formed non-uniformly (e.g., along the length of a stent) to provide a selected erosion sequence. As shown in Figs. 2-4, stent 28 can be configured to erode sequentially from its end portions 14, 16 to its middle segment 17 by making the thicknesses of outer and inner portions 20, 26 thinner at the end portions than at the middle segment, in embodiments in which the first material(s) reduces the erosion rate of erodible material. Referring particularly to Figs. 6A-6C, at end portions 14, 16, the thicknesses of outer and inner portions 20, 26 (T_{oe} and T_{ie}) can range from about 1 nm to about 750 nm The thicknesses of outer and inner portions 20, 26 can be the same or different. At middle segment 17, the thicknesses of outer and inner portions 20, 26 (T_{om} and T_{im}) can range from about 1 nm to about 750 nm. For each portion 14, 16, 17, the thicknesses of outer and inner portions 20, 26 can be the same or different. Alternatively or additionally to changing the thicknesses of inner and outer portions 20, 26 along stent 28, the chemical composition(s), including the concentration of first material, can be varied along the stent as described above to provide a desired erosion sequence.

For example, in other embodiments, stent 10 can be adapted to erode from a first end to a second end. For example, the thicknesses of outer and inner portions 20, 26 can increase (e.g., in a gradual taper) from end portion 14, along middle segment 17, to end portion 16. As a result, in embodiments in which the first material(s) increases the erosion rate of the erodible material, and the compositions of outer and inner portions 20, 26 are the same along the length of stent 10, the stent can erode sequentially from end portion 14 to end portion 16.

Referring to again Fig. 1B, the thickness of outer portion 26 (T_o) can range from about 1 nm to about 750 nm, e.g., from about 15 nm to about 500 nm, or from about 15 nm to about 100 nm. The thickness of middle portion 24 (T_m) can range from about 0.005 mm to about 2.0 mm, e.g., from about 0.05 mm to about 1.25 mm, or from about 0.05 mm to about 1.0 mm. The thickness of inner portion 26 (T_i) can range from about 1 nm to about 750 nm, e.g., from about 15 nm to about 500 nm, or from about 15 nm to about 100 nm.

A stent 10 can also be adapted to erode from a first end to a second end by forming, along the length of the stent, multiple, discrete segments having thicknesses for outer and inner portions 20, 26 that vary in step-wise fashion. Referring to Fig. 7, stent 50 includes three segments 52, 54, 56, each of which has an outer portion and an inner portion including a bioerodible material and one or more first materials. Each segment 52, 54, 56 has an erodible material between its outer and inner surfaces, similar to stent 10. In embodiments in which the first material(s) reduces the erosion rate of the bioerodible material, to erode sequentially from segment 52, to segment 54, to segment 56, the thicknesses of each outer and inner portions can increase from segment 52, to segment 54, to segment 56. For example, the thickness of the inner portion for segment 52 can be 10 nm, the thickness of the inner portion for segment 54 can be 50 nm, and the thickness of the inner portion for segment 56 can be 100 nm. The thicknesses of the inner portions, the outer portions and middle portion can be within the ranges provided above for T_i, T_o, and T_m. In other embodiments, only one of the portions 20, 26 varies along the stent, and the other portion can be constant or taper in thickness. A stent can have two segments, or more than three segments (e.g., four, five, six or more). Alternatively or additionally to varying the thicknesses of outer and inner portions 20, 26, the chemical compositions of the portions can be varied in step-wise fashion to effect a desired erosion sequence.

Referring now to Fig. 8, stent 50 can be produced from a metallic pre-stent 125 by employing system 80 shown in Fig. 5. During production, metallic pre-stent 125 is placed in system 80, where all portions of the pre-stent 125, including outer 130 and inner portions 132, are implanted with a selected species, e.g., oxygen or nitrogen. After a desired implantation time, an

implanted pre-stent 140 is removed from system 80. Implanted pre-stent 140 at this point has a transverse cross-section of segment 52 along its entire longitudinal length. Next, all exposed surfaces of segment 52 of implanted pre-stent 140 are covered with a coating, e.g., a protective polymeric coating, such as a styrene-isoprene-butadiene-styrene (SIBS) polymer, to produce a coated pre-stent 150. Coated pre-stent 150 is then placed back into system 80 and implanted with the desired species for the desired time, and then is removed from system 80, to produce a coated pre-stent 160. Conditions for implantation are selected to penetrate the desired species more deeply into pre-stent 150 than during formation of pre-stent 140. The coating on segment 52 protects this segment from additional implantation by the desired species. At this point, segment 52 of coated pre-stent 160 remains unchanged from pre-stent 140 (except for the protective coating), while the remaining portion of pre-stent 160 has a transverse cross-section of segment 54. Next, all exposed surfaces of segment 54 of pre-stent 160 are covered with a coating to produce a coated pre-stent 170. Coated pre-stent 170 is then placed back into system 80 and implanted with the desired species for the desired time, and then is removed from system 80, to produce a coated pre-stent 180. Conditions for implantation are selected to penetrate the desired species more deeply into pre-stent 170 than during formation of pre-stent 160. The coating on segments 52, 54 protects these segments from additional implantation by the desired species. At this point, coated pre-stent 180 has the desired transverse cross sections. The coatings can be removed, e.g., by rinsing with a solvent such as toluene, to complete the production of stent 50. A stent having tapered thicknesses can be produced by masking the interior and/or outer portions with a movable sleeve and longitudinally moving the sleeve and/or the stent relative to each other during implantation.

In use, the stents can be used, e.g., delivered and expanded, using a catheter delivery system, such as a balloon catheter system. Catheter systems are described in, for example, Wang U.S. 5,195,969, Hamlin U.S. 5,270,086, and Raeder-Devens, U.S. 6,726,712. Stents and stent delivery are also exemplified by the Radius® or Symbiot® systems, available from Boston Scientific Scimed, Maple Grove, MN.

The stents described herein can be of a desired shape and size (e.g., coronary stents, aortic stents, peripheral vascular stents, gastrointestinal stents, urology stents, and neurology stents). Depending on the application, the stent can have a diameter of between, for example, 1 mm to 46 mm. In certain embodiments, a coronary stent can have an expanded diameter of from about 2 mm to about 6 mm. In some embodiments, a peripheral stent can have an expanded diameter of from about 5 mm to about 24 mm. In certain embodiments, a gastrointestinal and/or urology stent can have an expanded diameter of from about 6 mm to about 30 mm. In some embodiments, a neurology stent can have an expanded diameter of from about 1 mm to about 12 mm. An abdominal aortic aneurysm (AAA) stent and a thoracic aortic aneurysm (TAA) stent can have a diameter from about 20 mm to about 46 mm. The stents can be balloon-expandable, or a combination of self-expandable and balloon-expandable (e.g., as described in U.S. Patent No. 5,366,504).

While a number of embodiments have been described above, the invention is not so limited.

As an example, the stents described herein can also be prepared using a laser-driven ion implantation process. Laser-driven ion implantation has been discussed by Yue, *Scripta Materialia*, 38(2), 191-198 (1998); and Schaaf, *Proceedings of SPIE*, vol. 5147, 404-415 (Bellingham, WA, 2003).

As another example, while the stents may have both outer and inner portions implanted with a desired species, in other embodiments, one or more segments of a stent may have only the outer portion or the inner portion implanted with the desired species. Outer portions of a pre-stent can be implanted with a desired species during PIII, e.g., by placing a mandrel, a pin or a sleeve that is sized to mate with the selected inner portion(s) of the pre-stent so that during plasma immersion, plasma is effectively blocked from entering inner portions of the pre-stent. Such a stent, after implantation, may have a transverse cross-section that has only two portions: an outer portion that is implanted with the desired species, and an inner portion that has not been implanted. Inner portions of a pre-stent can be implanted with a desired species during PIII, e.g., by placing a polymeric coating on selected outer portion(s) of the pre-stent so that during plasma immersion the desired species can penetrate only the inner

portions and is prevented from penetrating the outer portions. Alternatively, outer portions can be protected by placing the pre-stent in a tight-fitting tube, e.g., a heat shrink tube, to cover the outer portions.

In some embodiments, photo-lithography and/or stereo-lithography can be used to mask portions of a pre-stent to prevent implantation.

As another example, while outer and inner portions 20, 26 described herein include, respectively, the outer and inner surfaces of a stent, in other embodiments, one or both of the outer and inner portions are spaced from the outer and inner surfaces, respectively. For example, after one or both of outer and inner portions 20, 26 are formed, a second material can be disposed on one or both of the outer and inner portions, thereby forming a multi-layered stent in which the inner and/or outer portions having the first material(s) are spaced from the surfaces of the stent. The second material can be, for example, an erodible material, such as an erodible element, an erodible alloy, or an erodible polymer. This multi-layered construction can further allow the erosion of the stent to be controlled to provide a desired erosion profile over time.

In some embodiments, the corrosion rate of a bioerodible material can be increased by addition of one or more other materials. As an example, outer and inner portions 20, 26 of tubular body 13 can include an erodible combination of the erodible material of middle portion 24 and one or more first materials capable of increasing the erosion rate. For example, middle portion 24 can be formed of iron, and outer and inner portions 20, 26 can be formed of an alloy of iron and platinum.

Referring to Fig. 9, a multi-layered, erodible stent 190 may have more than two (e.g., three, four, five, six or more) outer and/or inner portions 20, 26. This multi-layered construction can provide a stent with an erosion profile resembling a square wave in which the erosion rates alternate between two (or more) different values.

In some embodiments, a stent can be configured to erode sequentially from an inner surface to an outer surface, or vice versa. Fig. 10 shows an erodible stent 201 having an inner layer 203, a middle layer 205, and an outer layer 207. The compositions and/or thicknesses of layers 203, 205, 207 can be selected as described above to selectively erode stent 201 from inner layer 203,

to middle layer 205, and then to outer layer 207. In some embodiments, outer layer 207 can include a non-erodible material, such as a plastically-deformable stainless steel or a superelastic, shape memory material (e.g., Nitinol). This construction allows the stent to support the body vessel initially using the strength of multiple layers, and to reduce in thickness over time (e.g., after cells have endothelialized the stent). The reduction in thickness can enhance the flexibility the stent to better match the natural state of the body vessel.

The stents described herein can be a part of a covered stent or a stent-graft. For example, a stent can include and/or be attached to a biocompatible, non-porous or semi-porous polymer matrix made of polytetrafluoroethylene (PTFE), expanded PTFE, polyethylene, urethane, or polypropylene.

The stents described herein can have non-circular transverse cross-sections. For example, transverse cross-sections can be polygonal, e.g., square, hexagonal or octagonal.

The stents described herein can include non-metallic structural portions, e.g., polymeric portions. The polymeric portions can be erodible. The polymeric portions can be formed from a polymeric alloy. Polymeric stents have been described in U.S. Patent Application Serial No. 10/683,314, filed October 10, 2003; and U.S. Patent Application Serial No. 10/958,435, filed October 5, 2004, the entire contents of each is hereby incorporated by reference herein.

The stents can include a releasable therapeutic agent, drug, or a pharmaceutically active compound, such as described in U.S. Patent No. 5,674,242, U.S.S.N. 09/895,415, filed July 2, 2001, U.S.S.N. 11/111,509, filed April 21, 2005, and U.S.S.N. 10/232,265, filed August 30, 2002. The therapeutic agents, drugs, or pharmaceutically active compounds can include, for example, anti-thrombogenic agents, antioxidants, anti-inflammatory agents, anesthetic agents, anti-coagulants, and antibiotics. The therapeutic agent, drug, or a pharmaceutically active compound can be dispersed in a polymeric coating carried by the stent. The polymeric coating can include more than a single layer. For example, the coating can include two layers, three layers or more layers, e.g., five layers. The therapeutic agent can be a genetic therapeutic agent, a non-genetic therapeutic agent, or cells. Therapeutic agents can be used singularly, or in combination. Therapeutic agents can be, for example, nonionic, or they may

be anionic and/or cationic in nature. An example of a therapeutic agent is one that inhibits restenosis, such as paclitaxel. The therapeutic agent can also be used, e.g., to treat and/or inhibit pain, encrustation of the stent or sclerosing or necrosing of a treated lumen. Any of the above coatings and/or polymeric portions can by dyed or rendered radio-opaque.

The stents described herein can be configured for non-vascular lumens. For example, it can be configured for use in the esophagus or the prostate. Other lumens include biliary lumens, hepatic lumens, pancreatic lumens, uretheral lumens and ureteral lumens.

Other configurations of stents are also possible. Referring to Fig. 11, a metallic coiled stent 200 has a straight portion 209 and a flared end portion 208. Flared end portion 208 can be have a lower overall erosion rate than straight portion 209, such that straight portion 209 erodes first in a lumen.

Referring to Fig. 12, a metallic coiled stent 206 has a straight portion 217 and a flared end portion 219. Stent 206 includes a plurality of protruding elements 210 that are integral with and extend outwardly from both portions 217 and 219 of stent 206. The friction provided by the protruding elements can help to hold stent 206 in place within, e.g., the prostatic urethra. Flared end portion 219 and straight portion 2107 can have similar overall erosion rates, while protruding elements 210 can have a lower overall erosion rate to allow the protruding elements to have a lifetime approaching that of the bulk stent 206, e.g., so that frictional control is maintained during the stent's lifetime.

Referring to Fig. 13, a metallic erodible wire stent 220 has bands 221 and connectors 223 that extend between and connect adjacent bands 221. Connectors 223 can be have a higher overall erosion rate than bands 221, such that connectors 223 erode first in a lumen. Such a configuration, e.g., enables greater flexibility of the stent as it erodes and ages.

Other embodiments are within the scope of the claims.

WHAT IS CLAIMED IS:

1. An endoprosthesis comprising a first metallic portion having a first erosion rate, and a second metallic portion having a second erosion rate different from the first erosion rate.

2. The endoprosthesis of claim 1, wherein the first and second metallic portions include a common metal.

3. The endoprosthesis of claim 1, wherein the common metal is magnesium, calcium, zinc or iron.

4. The endoprosthesis of claim 1, wherein at least one of the metallic portions is substantially a pure metal.

5. The endoprosthesis of claim 1, wherein the first metallic portion includes an outside surface or an inside surface of the endoprosthesis, and wherein the second metallic portion is disposed inwardly of the first portion.

6. The endoprosthesis of claim 1, wherein the first and second metallic portions are circular in a transverse cross-section of the endoprosthesis.

7. The endoprosthesis of claim 1, wherein the metallic portions include a metallic alloy.

8. The endoprosthesis of claim 1, wherein a thickness of the metallic portion having a lower erosion rate is from about 10 nm to about 1000 nm.

9. The endoprosthesis of claim 8, wherein the thickness is from about 15 nm to about 100 nm.

10. The endoprosthesis of claim 1, wherein the erosion rate of the metallic portion having a lower erosion rate is from about 0.01 percent of an initial mass of that portion per day to about 1 percent of the initial mass of that portion per day.

11. The endoprosthesis of claim 10, wherein the erosion rate is from about 0.1 percent of the initial mass of that portion per day to about 0.5 percent of the initial mass of that portion per day.

12. The endoprosthesis of claim 1, wherein the erosion rate of the metallic portion having a higher erosion rate is from about 0.2 percent of an

initial mass of that portion per day to about 10 percent of the initial mass of that portion per day.

13. The endoprosthesis of claim 12, wherein the erosion rate is from about 0.5 percent of the initial mass of that portion per day to about 5 percent of the initial mass of that portion per day.

14. The endoprosthesis of claim 1, wherein the erosion rate of the metallic portion having the higher erosion rate is from about ten percent to about one-hundred percent greater than the erosion rate of the metallic portion having the lower erosion rate.

15. The endoprosthesis of claim 1, wherein the first and second metallic portions are disposed within a longitudinal segment of the endoprosthesis.

16. The endoprosthesis of claim 1, wherein the endoprosthesis includes a plurality of segments, at least two of the segments having different erosion rates.

17. The endoprosthesis of claim 16, wherein at least two of the segments are arranged along a longitudinal length of the endoprosthesis.

18. The endoprosthesis of claim 1, wherein the endoprosthesis is adapted to erode sequentially along a longitudinal length of the endoprosthesis.

19. The endoprosthesis of claim 1, wherein the endoprosthesis is adapted to erode sequentially along a direction transverse to the longitudinal length of the endoprosthesis.

20. The endoprosthesis of claim 1, comprising an inner surface, an outer surface, and a portion between the inner and outer surfaces, wherein the portion between the inner and outer surfaces has an erosion rate higher than an erosion rate of the inner surface or the outer surface.

21. The endoprosthesis of claim 1, wherein the endoprosthesis is tubular in form.

22. The endoprosthesis of claim 1, wherein the endoprosthesis comprises a stent.

23. A method of making an endoprosthesis, the method comprising:

implanting a material into a first portion of an erodible endoprosthesis, wherein the implanted first portion has a higher concentration of the first material than a second portion of the endoprosthesis.

24. The method of claim 23, wherein the first portion has a different erosion rate than the second portion.

25. The method of claim 23, wherein the implanting employs a plasma.

26. The method of claim 23, wherein the implanted material comprises an element selected from the group consisting of nitrogen, carbon, silicon, oxygen, sulfur, chromium, silver, gold, boron, and mixtures thereof.

27. The method of claim 23, wherein the erodible endoprosthesis includes a metallic material selected from the group consisting of magnesium, calcium, lithium, rare earth elements, iron, aluminum, zinc, manganese, cobalt, copper, zirconium, titanium, and mixtures thereof.

28. The method of claim 23, further comprising, prior to implanting, applying a shielding to a portion of the endoprosthesis.

29. The method of claim 28, wherein the shielding comprises a coating.

30. The method of claim 29, wherein the coating comprises a polymer.

31. The method of claim 28, further comprising, after implanting, removing the applied shielding.

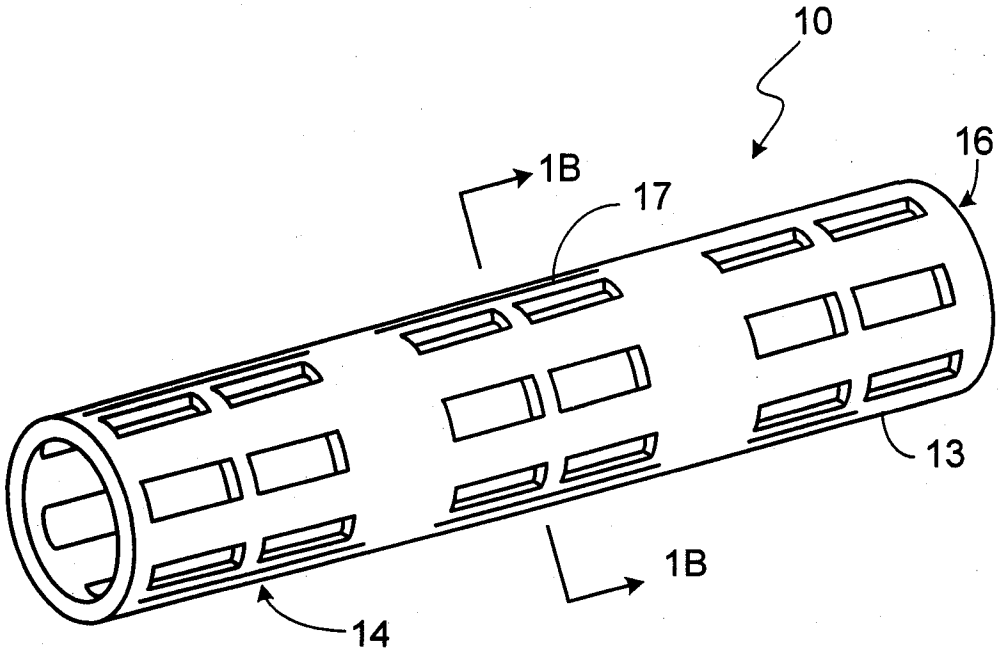


FIG. 1A

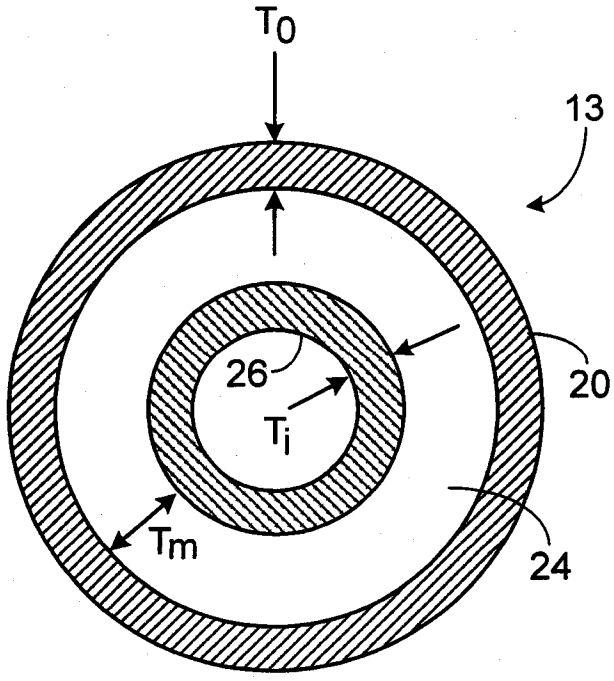


FIG. 1B

FIG. 2

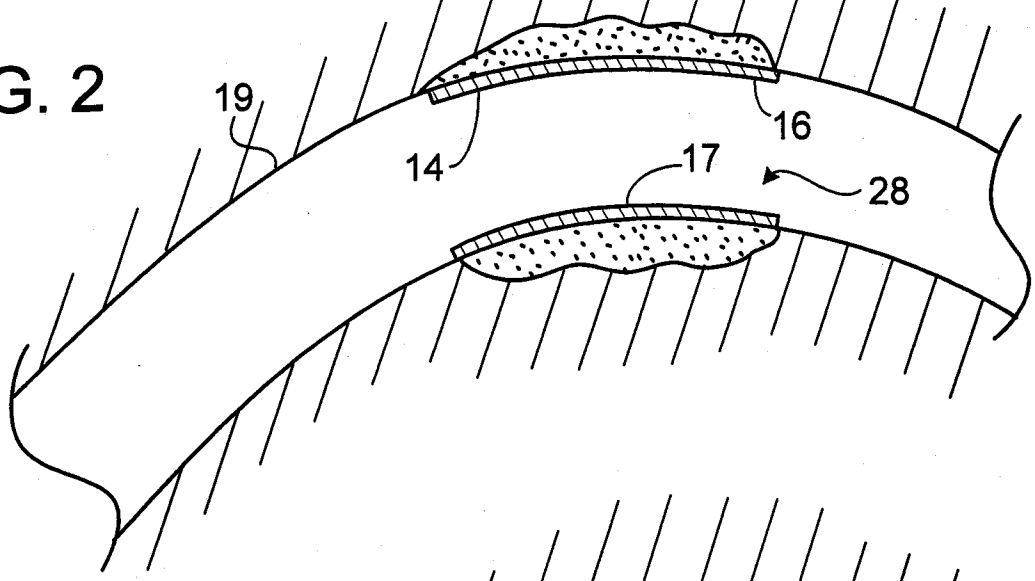


FIG. 3

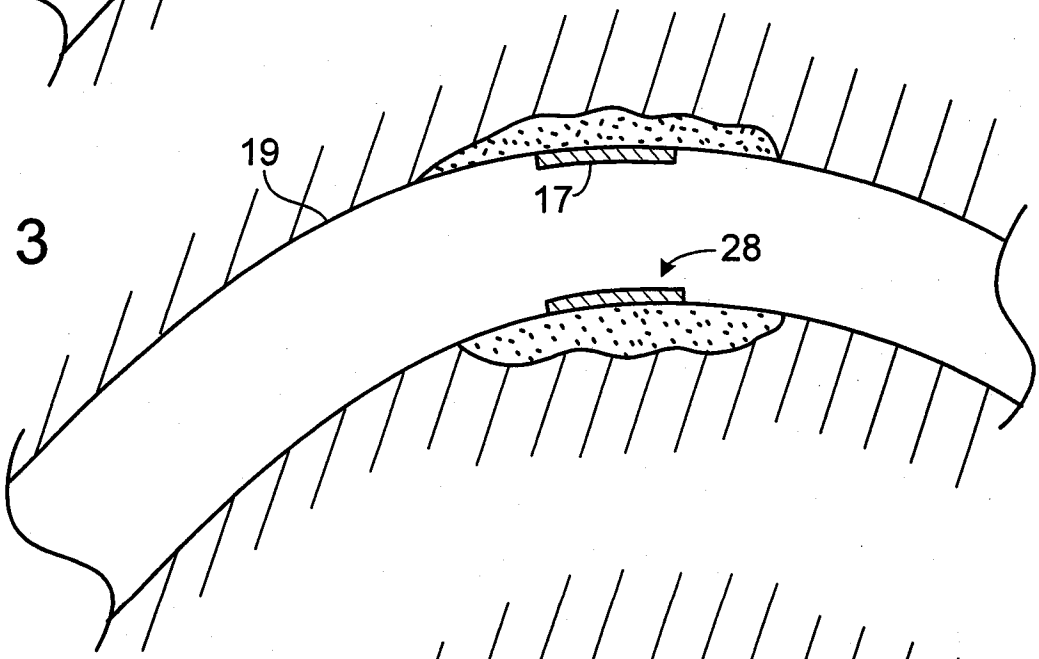
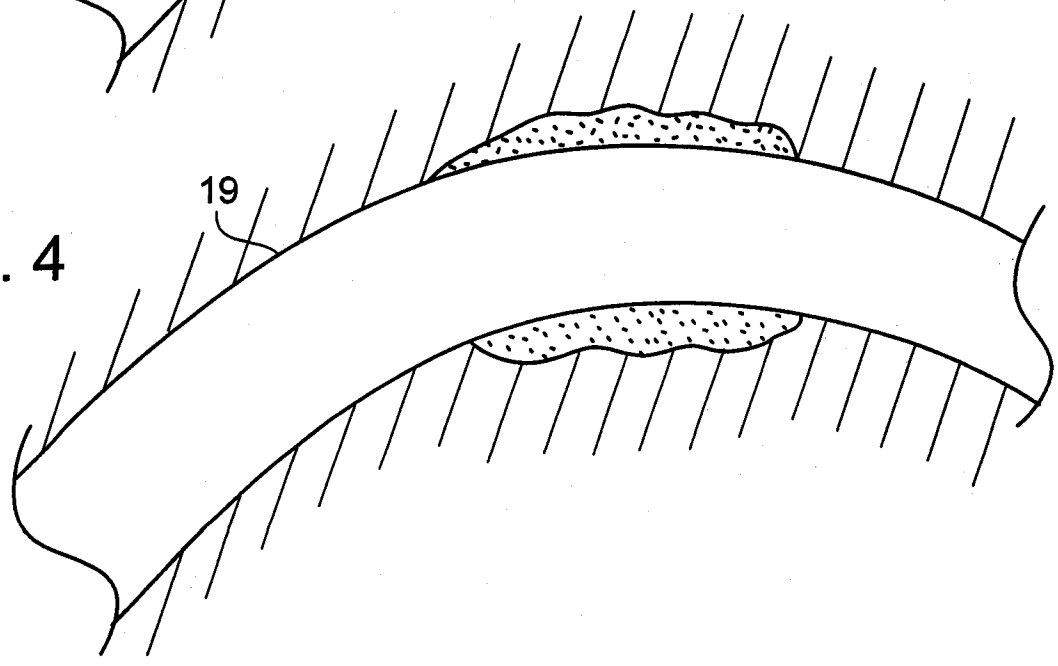


FIG. 4



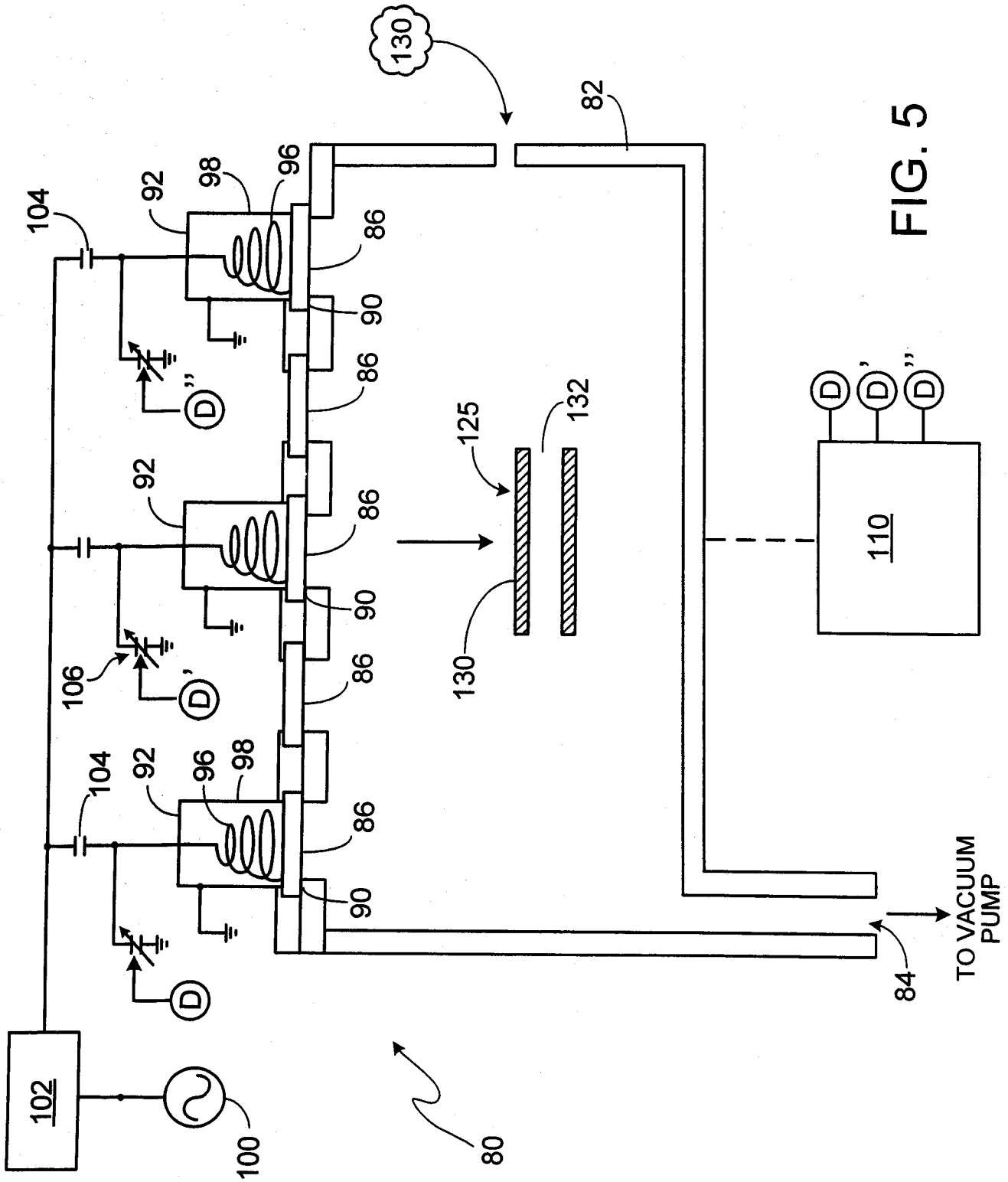

130
82
104
92
98
96
86
90
D''
125
132
D
D'
D''
110
106
D'
130
TO VACUUM PUMP
84
102
100
80

FIG. 5

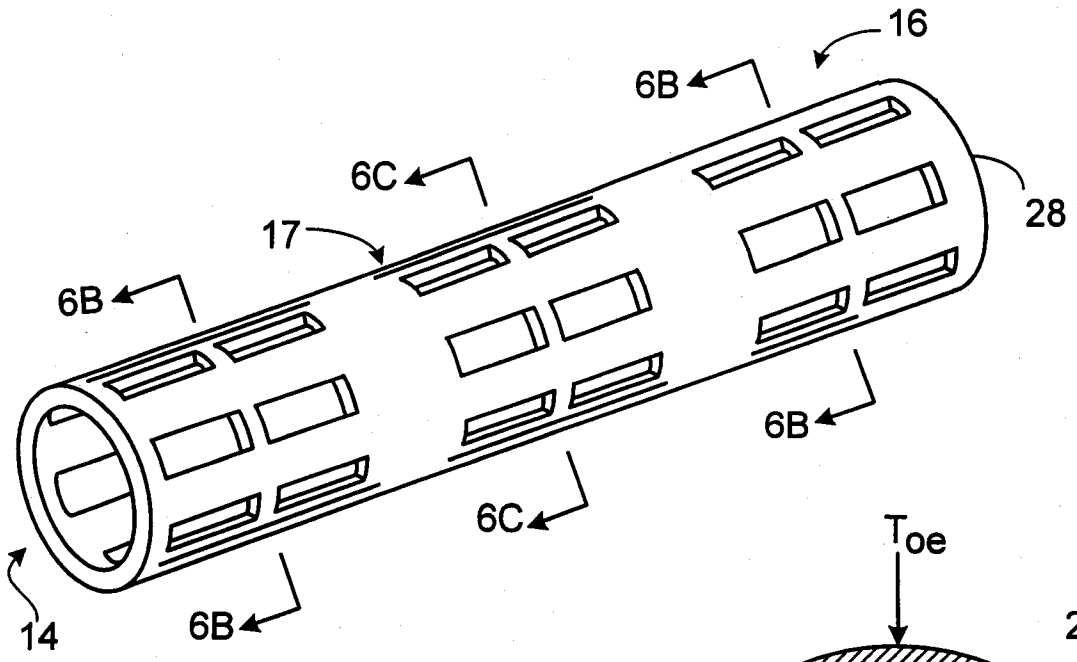


FIG. 6A

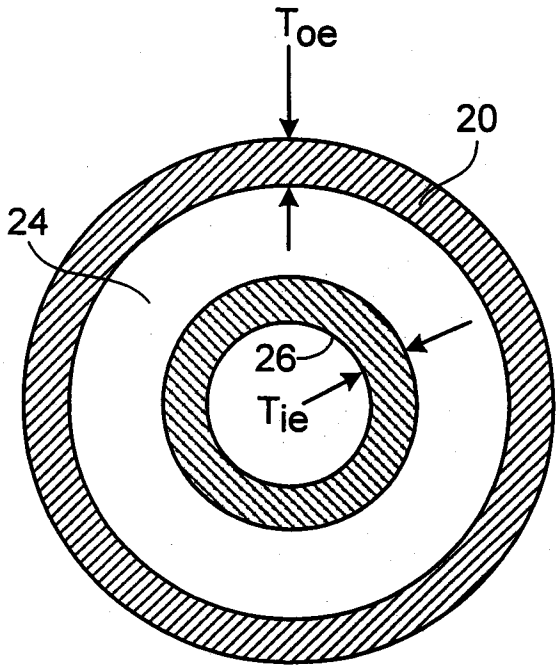


FIG. 6B

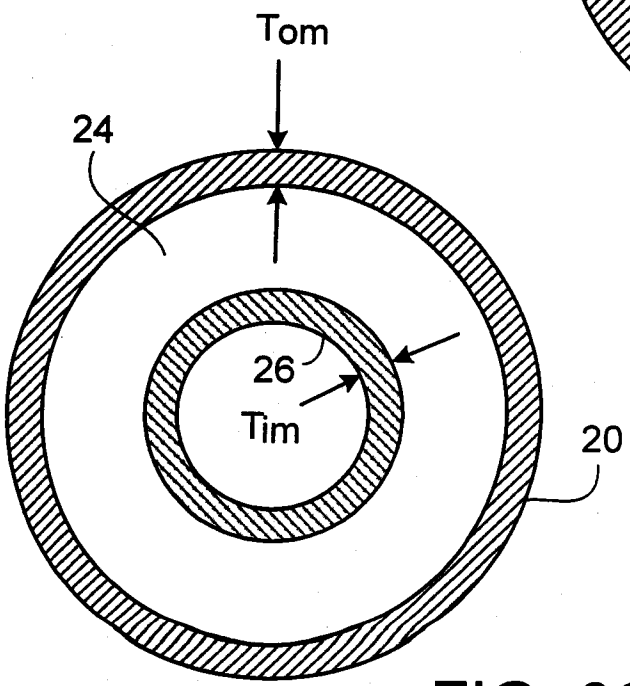


FIG. 6C

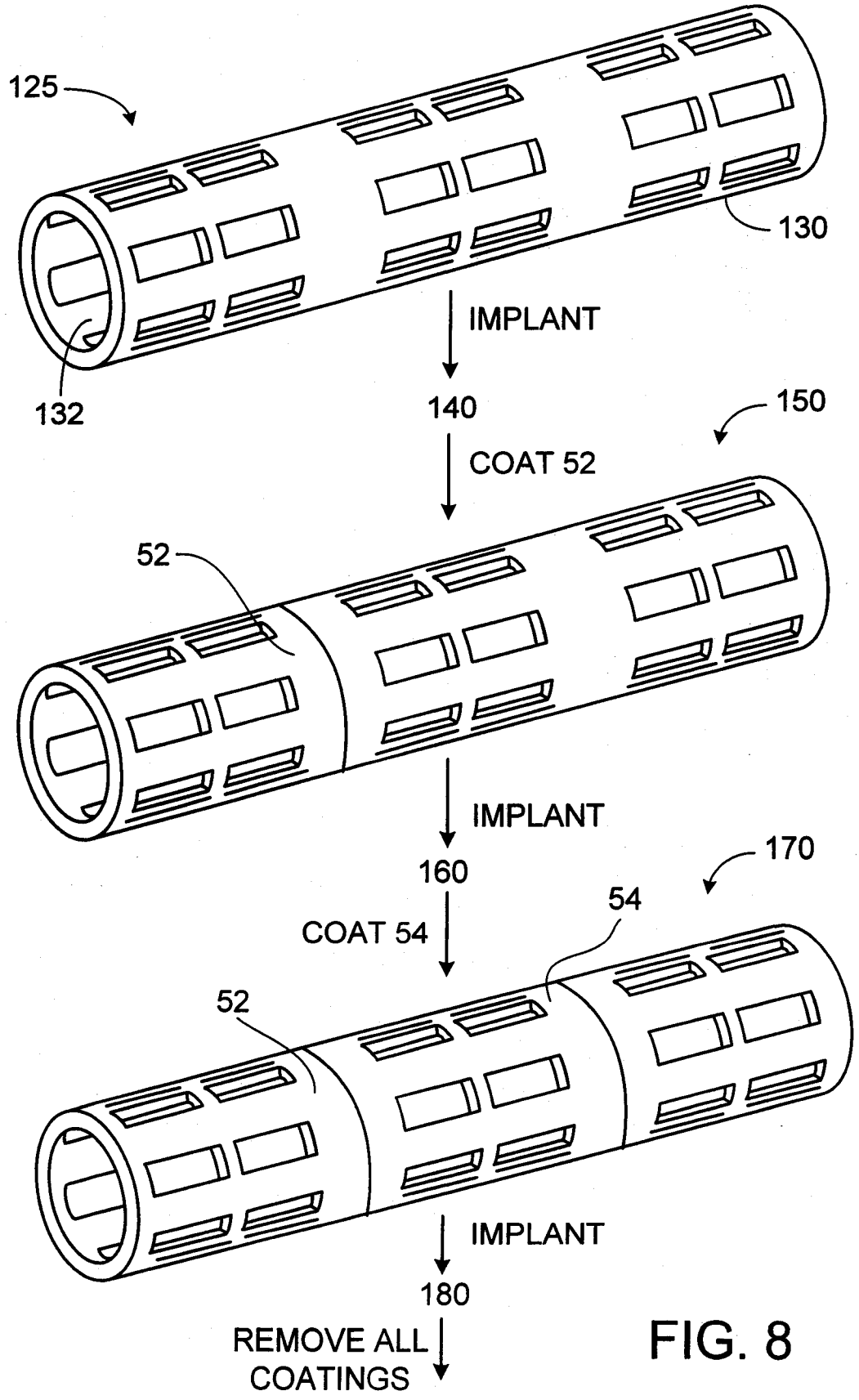

125
130
IMPLANT
132
140
150
COAT 52
52
IMPLANT
160
170
COAT 54
54
52
IMPLANT
180
REMOVE ALL COATINGS

FIG. 8

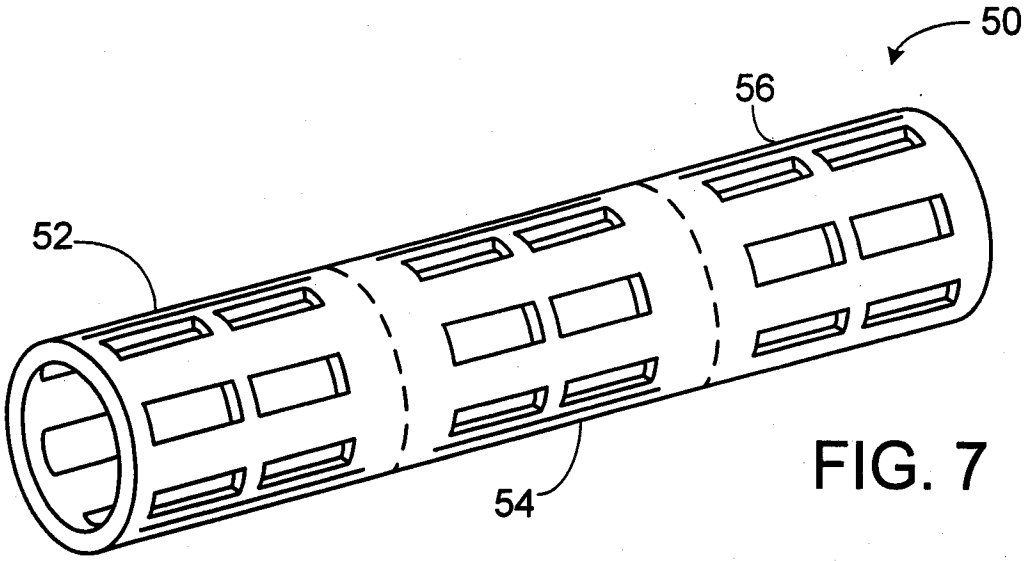


FIG. 7

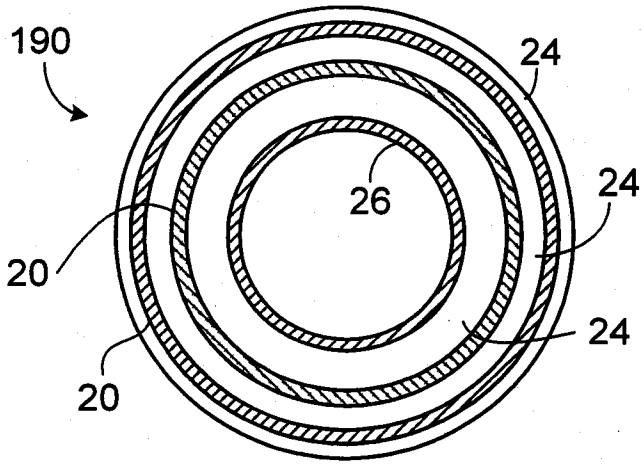


FIG. 9

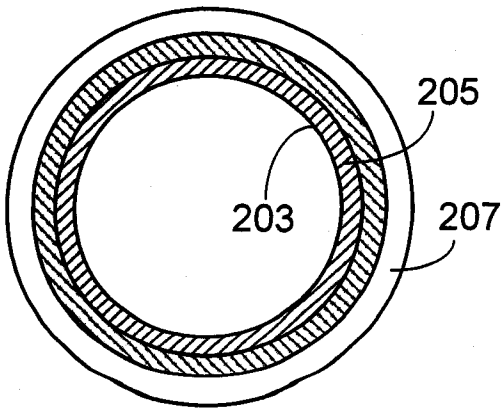


FIG. 10

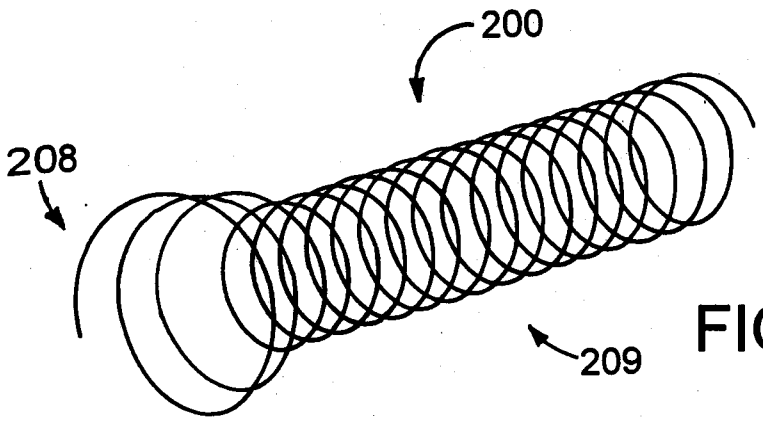


FIG. 11

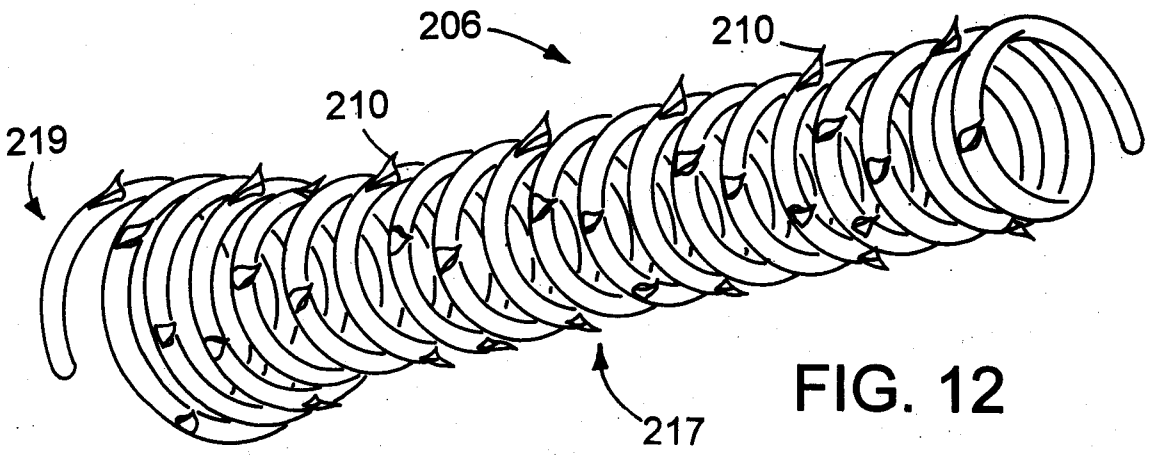


FIG. 12

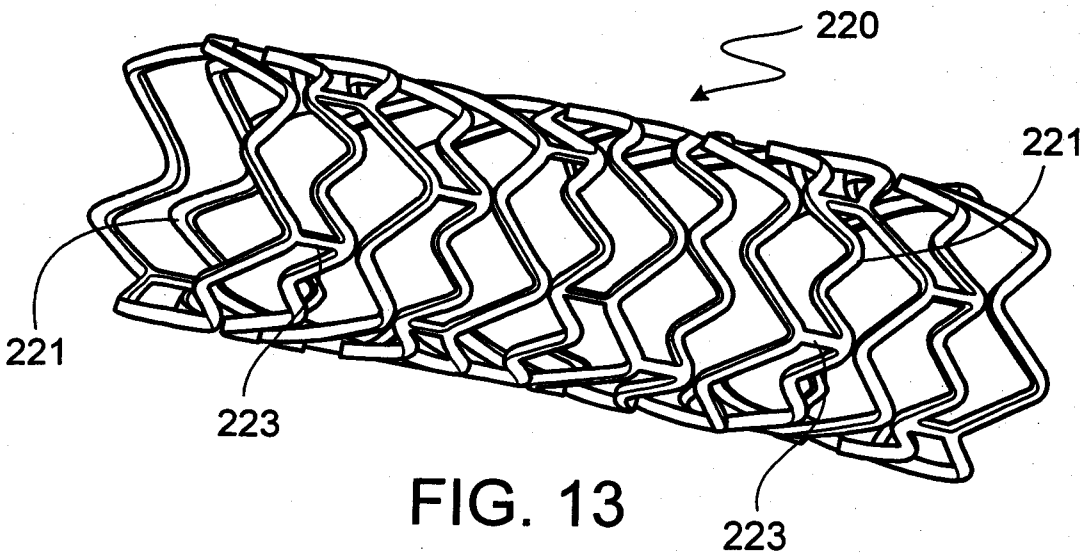


FIG. 13