(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 July 2005 (21.07.2005)

PCT

(10) International Publication Number
WO 2005/065280 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/US2004/043455

(22) International Filing Date:
23 December 2004 (23.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/746,563 24 December 2003 (24.12.2003) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

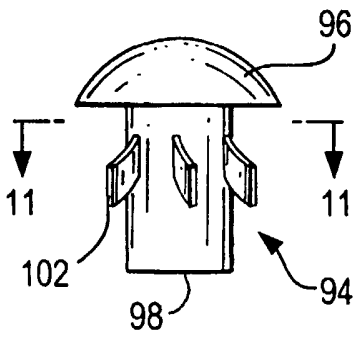
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: REPAIR OF SPNAL ANNULAR DEFECTS AND ANNULO-NUCLEOPLASTY REGENERATION



(57) Abstract: The invention relates to the repair of spinal annular defects. An appartatus comprises a scaffold comprised of a biodurable, resiliently compressible, elastomeric reticulated composition to obliterate spinal/vertabral connective tissue defects, to obliterate spinal-annular nuclear tissue defects, and for spinal annulonucleoplasty regeneration. The apparatus comprises an at least partially cylindrical member.

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REPAIR OF SPINAL ANNULAR DEFECTS AND ANNULO-NUCLEOPLASTY REGENERATION

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is based upon co-pending, commonly assigned U.S. Patent Application Serial No. 10/746,563, filed December 24, 2003, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] This invention relates to the repair of spinal annular defects. More particularly, this invention relates to a method and composition for the repair of spinal annular defects and annulo-nucleoplasty regeneration.

BACKGROUND OF THE INVENTION

[0003] Back pain is one of the most common and often debilitating conditions affecting millions of people. Some forms of back pain are muscular in nature and may be simply treated by rest, posture adjustments and painkillers. For example, lower back pain (LBP) is a very common condition that may be caused by unusual exertion or injury. Unusual exertion such as heavy lifting or strenuous exercise may result in back pain due to a pulled muscle, a sprained muscle, a sprained ligament, a muscle spasm, or a combination thereof. An injury caused by falling down or a blow to the back may cause bruising. These forms of back pain are typically non-chronic and may be self-treated and cured in a few days or weeks.

[0004] Other types of non-chronic back pain may be treated by improvements in physical condition, posture and/or work conditions. Being pregnant or otherwise being significantly overweight may cause LBP. A mattress that does not provide adequate support may cause back pain in the morning. Working in an environment lacking good ergonomic design may also cause back pain. In these instances, the back pain may be cured by eliminating the underlying cause. Whether it is excess body

weight, a bad mattress, or a bad office chair, these forms of back pain are readily treated.

[0005] It is estimated that over ten million people in the United States alone suffer from persistent back pain. Approximately half of those suffering from persistent back pain are afflicted with chronic disabling pain, which seriously compromises a person's quality of life and is the second most common cause of worker absenteeism. Further, the cost of treating chronic back pain is very high, even though the majority of sufferers do not receive treatment due to health risks, limited treatment options, and/or inadequate therapeutic results. Thus, chronic back pain has a significantly adverse effect on a person's quality of life, on industrial productivity, and on heath care expenditures.

[0006] Some forms of back pain are the result of disorders directly related to the spinal column, which disorders are not readily treated. While some pain-causing spinal disorders may be due to facet joint degradation or degradation of individual vertebral masses, disorders associated with the intervertebral discs are predominantly affiliated with chronic back pain (referred to as disc related pain). The exact origin of disc related pain is often uncertain, and although some episodes of disc related pain may be eased with conservative treatments such as bed-rest and physical therapy, future episodes of disc related pain are likely to occur periodically.

[0007] There are a number of suspected causes of disc related pain, and in any given patient, one or more of these causes may be present. However, the ability to accurately diagnose a specific cause or locus of pain is currently difficult. Because of this uncertainty, many of the causes of disc related pain are often lumped together and referred to as degenerative disc disease (DDD).

[0008] A commonly suspected source of disc related pain is physical impingement of the nerve roots emanating from the spinal cord. Such nerve root impingement may have a number of different underlying causes, but nerve root

impingement generally results from either a disc protrusion or a narrowing of the intervertebral foramina (which surround the nerve roots).

[0009] As a person ages, their intervertebral discs become progressively dehydrated and malnourished. Due to the combination of aging and continued stressing, the discs begin to degenerate. With continued degeneration, or an excessive stressing event, or both, the annulus fibrosus of a disc may tear, forming one or more fissures (also referred to as fractures). Such fissures may progress to larger tears, which allow the gelatinous material of the nucleus pulposus to flow out of the nucleus and into the outer aspects of the annulus. The flow of the nucleus pulposus to the outer aspects of the annulus may cause a localized bulge or herniation.

[0010] When herniation of the nucleus/annulus occurs in the posterior portions of the disc, nerve roots may be directly and physically impinged by the bulge. In more extreme or progressed instances of annular tears, the nuclear material may escape, additionally causing chemical irritation of the nerve roots. Dependent upon the cause and nature of the disc protrusion, the condition may be referred to as a disc stenosis, a disc bulge, a herniated disc, a prolapsed disc, a ruptured disc, or, if the protrusion separates from the disc, a sequestered disc.

[0011] Dehydration and progressive degeneration of a disc also leads to thinning of the disc. As the thickness of the disc reduces, the intervertebral foraminae become narrow. Because the nerve roots pass through the intervertebral foraminae, such narrowing may mechanically entrap the nerve roots. This entrapment can cause direct mechanical compression or it may tether the roots, causing excessive tension to the roots during body movement.

[0012] Nerve root impingement most often occurs in the lumbar region of the spinal column since the lumbar discs bear significant vertical loads relative to discs in other regions of the spine. In addition, disc protrusions in the lumbar region typically occur posteriorly because the annulus fibrosus is radially thinner on the posterior side

than on the anterior side and because normal posture places more compression on the posterior side. Posterior protrusions are particularly problematic since the nerve roots are posteriorly positioned relative to the intervertebral discs. Lower back pain due to nerve root irritation not only results in strong pain in the region of the back adjacent the disc, but may also cause sciatica, or pain radiating down one or both legs. Such pain may also be aggravated by such subtle movements as coughing, bending over, or remaining in a sitting position for an extended period of time.

[0013] Another suspected source of disc related back pain is damage and irritation to the small nerve endings which lie in close proximity to or just within the outer aspects of the annulus of the discs. Again, as the disc degenerates and is subjected to stressing events, the annulus fibrosus may be damaged and form fissures. While these fissures can lead to pain via the mechanisms described above, they may also lead to pain emanating from the small nerve endings in or near the annulus, due to mechanical or chemical irritation at the sites of the fissures. The fissures may continue to irritate the small nerve endings, as their presence causes the disc to become structurally weaker, allowing for more localized straining around the fissures. This results in more relative motion of edges of the fissures, increasing mechanical irritation. Because it is believed that these fissures have only limited healing ability once formed, such irritation may only become progressively worse.

[0014] A common treatment for a disc herniation is a discectomy, a procedure wherein the protruding portion of the degenerated disc is surgically removed. However, discectomy procedures have an inherent risk since the portion of the disc to be removed is immediately adjacent the nerve root, and any damage to the nerve root is clearly undesirable. Furthermore, discectomy procedures are not always successful long term because scar tissue may form and/or additional disc material may subsequently protrude or reherniate from the disc space as the disc deteriorates further. The recurrence of a disc herniation may necessitate a repeat discectomy procedure, along with its inherent clinical risks and less than perfect long term success

rate. Thus, a discectomy procedure, at least as a stand-alone procedure, is clearly not an optimal solution.

[0015] Discectomy is also not a viable solution for DDD when no disc/nuclear herniation is involved. As mentioned above, DDD causes the entire disc to degenerate, narrowing the intervertebral space and shifting the load to the facet joints. If the facet joints carry a substantial load, the joints may degrade over time and be a different cause of back pain. Furthermore, the narrowed disc space can result in the intervertebral foramina surrounding the nerve roots directly impinging on one or more nerve roots. Such nerve impingement is very painful and cannot be corrected by a discectomy procedure. Furthermore, a discectomy does not address pain caused by annular fissures or post-surgical defects, which may cause direct mechanical irritation to the small nerve endings near or just within the outer aspect of the annulus of a damaged disc.

[0016] As a result of the limitations of a discetomy, spinal fusion, particularly with the assistance of interbody fusion cages, has become a preferred secondary procedure, and in some instances, a preferred primary procedure. Spinal fusion involves permanently fusing or fixing adjacent vertebrae. Hardware in the form of bars, plates, screws, and cages may be utilized in combination with bone graft material to fuse adjacent vertebrae. Spinal fusion may be performed as a stand-alone procedure, or it may be performed in combination with a discectomy procedure. By placement of the adjacent vertebrae in their normal position and fixing them in place, relative movement therebetween may be significantly reduced and the disc space may be restored to its normal condition. Thus, theoretically, aggravation caused by relative movement between adjacent vertebrae may be reduced if not eliminated.

[0017] The success rate of spinal fusion procedures is certainly less than perfect for a number of different reasons, none of which are well understood. In addition, even if spinal fusion procedures are initially successful, they may cause accelerated degeneration of adjacent discs since the adjacent discs must accommodate a greater

degree of motion. The degeneration of adjacent discs simply leads to the same problem at a different anatomical location, which is clearly not an optimal solution. Furthermore, spinal fusion procedures are invasive to the disc, risk nerve damage, and, dependent upon the procedural approach, are technically complicated (endoscopic anterior approach), invasive to the bowel (surgical anterior approach), and/or invasive to the musculature of the back (surgical posterior approach).

[0018] Another procedure that has been less than clinically successful is total disc replacement with a prosthetic disc. This procedure is also very invasive to the disc, and, dependent upon the procedural approach, either invasive to the bowel (surgical anterior approach) or invasive to the musculature of the back (surgical posterior approach). In addition, the procedure may actually complicate matters by creating instability in the spine, and the long-term mechanical reliability of prosthetic discs has yet to be demonstrated.

[0019] Many other medical procedures have been proposed to solve the problems associated with degenerative discs or disc protrusions. However, many of the proposed procedures have not been clinically proven, and some of the allegedly beneficial procedures have controversial clinical data. There is a substantial need for improvements in the treatment of spinal disorders, particularly in the treatment of disc related pain associated with a damaged or otherwise unhealthy disc, specifically the repair of disc defects or annulo-nucleoplasty regeneration.

OBJECTS OF THE INVENTION

[0020] It is an object of the invention to provide a method for the repair of spinal annular defects.

[0021] It is also an object of the invention to provide a composition for the repair of spinal annular defects.

[0022] It is a further object of the invention to provide a method and

composition for annulo-nucleoplasty regeneration.

[0023] It is a yet further object of the invention to provide a method of repairing spinal annular defects where a polymeric or metallic substantially cylindrical member is inserted into the spinal annulus.

[0024] It is a yet further object of the invention where a polymeric or metallic substantially cylindrical member is inserted into the spinal annulus to promote annulo-nucleoplasty regeneration.

[0025] These and other objects of the invention will become more apparent from the discussion below.

SUMMARY OF THE INVENTION

[0026] The invention described and claimed below relates to the repair of spinal annular defects. According to the invention, a substantially cylindrical member is inserted through an opening in the spinal annulus to the extent that the distal portion of the substantially cylindrical member extends into the spinal nuclear defect. The substantially cylindrical member is comprised of a biodurable reticulated elastomeric material that expands to seal the opening. Optionally the cylindrical member can comprise one or more metal or polymer components that open or re-align after insertion to assist in maintaining the sealing ability of the substantially cylindrical member.

[0027] The present invention addresses this need by providing improved devices and methods for the treatment of spinal disorders. The improved devices and methods of the present invention specifically address disc related pain, progressive disc degeneration, and/or reherniation of nuclear material, particularly in the lumbar region, but may have other significant applications not specifically mentioned herein. For purposes of illustration only, and without limitation, the present invention is discussed in detail with reference to the treatment of damaged discs in the lumbar

region of the adult human spinal column. Optionally, the device may be used for damaged discs in the thoracic and cervical region of the adult human spinal column

[0028] As will become apparent from the detailed description below, the improved devices and methods of the present invention reduce, if not eliminate, back pain while maintaining near normal anatomical motion. Specifically, the present invention provides an annular repair and/or annulo-nucleoplasty regeneration mechanism, while permitting relative movement of the vertebrae adjacent the damaged disc. The devices of the present invention are particularly well suited for minimally invasive methods of implantation.

[0029] The devices of the present invention provide three distinct functions. First, the reinforcement devices mechanically stabilize and strengthen the annular portion of the spinal disc to minimize, if not eliminate, chronic irritation of local nerve roots and nerve endings adjacent to the periphery of the disc annulus. Second, the devices radially and/or circumferentially conform to the surgical and/or pathologic present fissures, fractures,and tears of the disc, thereby preventing the prolapse of extra spinal disc tissue such as nerves and muscle, thereby potentially facilitating healing. And third, the devices may be used to stabilize the nuclear portion of the disc after a discectomy procedure to reduce the need for a subsequent operation or treatment due to reherniation.

[0030] In an exemplary embodiment, the present invention provides disc reinforcement in which a device of the invention is implanted into the annulus of an intervertebral disc. The implantation method may be performed by a percutaneous procedure or by a minimally invasive surgical procedure or by the use of trocar, cannula, or through an endoscopic instrument such as an arthroscope, laproscope, or cystoscope. The present invention provides a number or tools to facilitate percutaneous implantation. One or more reinforcement members may be implanted, for example, posteriorly, anteriorly, and/or laterally, and may be oriented circumferentially or radially. As such, the reinforcement members may be used to

stabilize the annulus and/or a portion of the annulus so as to reduce recurrent bulges and/or obliterate annular tracts.

[0031] The implant device may be sized to pass through a trocar and/or may have a tubular cross-section to facilitate advancement over a stylet. The implant device preferably includes a body portion sized to fit in an opening in the annulus and an anchor for engaging the annulus and limiting relative movement therebetween. The anchor may be disposed at the distal portions of the implant body, or may extend over the entire length of the body. The anchoring part to engage in the annulus can be shaped as expanded cylinder, spherical, mushroom-shaped, etc. The anchor portion may comprise threads or wings which may have a variable pitch to facilitate compression of the annulus during implantation. The implant device may incorporate chemical and/or biological agents. The implant device may comprise a biocompatible metal such as stainless steel or a super elastic (nickel titanium) alloy. Alternatively, the implant device may comprise a polymer or a reinforced polymeric structure. As a further alternative, the implant device may comprise a bioabsorbable material.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] Fig. 1 illustrates a superior (top) view of a healthy disc;

[0033] Figs. 2 and 3 each illustrate a superior (top) view of a degenerated disc;

[0034] Fig. 4 is a partially cross-sectional view of an embodiment of a substantially cylindrical member according to the invention;

[0035] Fig. 5 is a partially cross-sectional view of an embodiment of an at least partially cylindrical member according to the invention;

[0036] Fig. 6 is a partially cross-sectional view of a further embodiment of another at least partially cylindrical member according to the invention;

[0037] Fig. 7 is a cross-sectional view across the line 7-7 of the embodiment of the invention shown in Fig. 6;

[0038] Fig. 8 is a partially cross-sectional view of another embodiment of the invention in position in the annulus;

[0039] Fig. 9 is a partially cross-sectional view of a variation of the embodiment shown in Fig. 8;

[0040] Fig. 10 is a lateral view of an embodiment of the invention having radial projections;

[0041] Fig. 11 is a cross-sectional view along the line 11-11 in Fig. 10;

[0042] Figs. 12 to 14 represent cross-sectional views of delivery of the embodiment of the invention set forth in Figs. 10 and 11;

[0043] Figs. 15 and 16 are each a micrograph of material prepared according to Example 1;

[0044] Figs. 17 and 18 are each a micrograph of material prepared according to Example 2;

[0045] Fig. 19 is a micrograph of an embodiment of the invention four weeks after placement; and

[0046] Fig. 20 is a detailed view of a section of the micrograph in Fig. 19.

DETAILED DESCRIPTION OF THE INVENTION

[0047] The invention can perhaps be better appreciated from the drawings. Figure 1 is a simplified representation of a spinal disc 10 that comprises an annulus fibrosis or annulus 12 surrounding a nucleus pulposus or nucleus 14. The posterior annulus 16 is generally thinner than the anterior annulus 18, which may account for the higher incidence of posterior disc protrusions.

[0048] A common theory is that each intervertebral disc 10 forms one support point and the facet joints of the spinal column (not shown) form two support points of what may be characterized as a three-point support structure between adjacent vertebrae 20. However, in the lumbar region, the facet joints are substantially vertical, leaving the disc 10 to carry the vast majority of the load. As between the annulus 12 and the nucleus 14 of the disc 10, it is commonly believed that the nucleus 14 bears the majority of the load. This belief is based on the theory that the disc 10 behaves much like a balloon or tire and the nucleus 14 bears the somewhat of the majority of the load wherein the annulus 12 merely serves to contain the pressurized nucleus 14 and supports a somewhat smaller proportion of the total load. The annulus 12 comprises 60% of the total disc 10 cross-sectional area and is made of 40-60% organized collagen in the form of a laminated structure. By contrast, the nucleus 14 only comprises 40% of the total disc 10 cross-section and is made of 18-30% collagen in the form of a relatively homogenous gel. In reality, both the nucleus 14 and annulus 12 play important and critical roles in the load bearing mechanism of the disc 10.

[0049] The intervertebral disc 10 becomes progressively dehydrated and malnourished with age, as shown in Figures 2 and 3. In combination with continued stressing from load bearing and/or resisting outward pressure from the nucleus, the disc begins to degenerate. With continued degeneration, or an excessive stressing event, the annulus of the disc may tear, forming one or more radial fissures 23 or tracts 24 or circumferential fissures 26, which may progress to larger tears. Larger

tears may allow the gelatinous material of the nucleus pulposus 14 to flow out of the nucleus through a fissure 24 and into the outer aspects of the annulus 12. Nuclear material that escapes through an advanced tear may cause further mechanical irritation and additionally cause chemical irritation of a nerve root.

[0050] The flow of the nucleus 14 to the outer aspects of the annulus 12 may cause a localized bulge 28. A posterior bulge 28 may result in direct impingement of a nerve root (not shown).

[0051] A nerve root may also be compressed or tethered by a narrowing of the intervertebral foraminae, resulting from a loss in disc height caused by sustained degeneration of the disc 10. Small nerve endings (not shown) in or near the perimeter of the annulus 12 may also be mechanically or chemically irritated at the sites of the fissures 24, 26. In all cases, degeneration of the disc eventually leads to disc related pain of some origin.

[0052] In an embodiment of the invention shown in Figure 4, a partially cylindrical device 30 comprises a cylindrical portion 32 and an attached expanded, at least partially spherical portion 34. Portion 34 may be entirely spherical or it may optionally have a substantially flat surface 36 bordered by edge 38. Optionally, the attached expanded portion 34 may be entirely cylindrical. In one embodiment, the attached expanded portion 34 may be any other suitable shape that has at least one transverse dimension larger than the diameter of the cylindrical portion 32. Portions 32 and 34 are both solid, although optionally each may contain a longitudinal lumen (not shown) to facilitate threading member 30 over a wire or stylet (not shown). Also, device 30 may optionally contain a retainer or anchor 40, comprising a longitudinal member or shaft 42 and collapsible/expandable spokes or radial members 44. Preferably the proximal end of each member 44 has a tissue fixation member 46 that contacts the inner portion of the annulus when members 44 expand, to hold or fix device 30 in position.

[0053] The umbrella anchor 40 is has three or four, preferably four, members 44 and a central shaft 42 as shown in Fig. 4. The members 44 can be partially collapsed within a trocar or endoscope during delivery and contact the inner portion of the annulus when they expand after delivery to hold or fix elastomeric reticulated device 30 or device 48 in position.

[0054] Anchor 40 can have a range of dimensions depending on specific applications. The range of dimensions of the different parts are as follows: the angle between central shaft 42 and spokes 44 is from about 15° to about 60°, when the spokes are fully opened. The length of each spoke 44 ranges from about 3 mm to about 10 mm, preferably from about 4 mm to about 7 mm. The cross-section of spokes 44 can be cylindrical, elliptical, square, rectangular, or any other polygonal shape. The diameter of spokes' 44 cross-section or one side of the spoke 44 cross-section ranges from about 2 mm to about 5 mm. The end-to-end distance of the spokes 44 when the spokes 44 are fully opened ranges from about 6 mm to about 15 mm. The cross-section of central shaft 42 can be cylindrical, elliptical, square, rectangular, or any other polygonal shape with the diameter of the central shaft 42 cross-section or one side of the of the central shaft cross-section ranging from about 2 mm to about 5 mm. The overall length of central shaft 42 of the umbrella anchor (including the head and the stem) can range from about 8 mm to about 15 mm.

[0055] Spokes 44 can be regularly spaced from each other or they could be "paired" as cross-pieces. For example, adjacent spokes 44 could be separated by 60° and 120° to form an "X" pattern. Also, in another embodiment, shaft 42 could extend in the direction from spokes 44 opposite to the direction shown in Fig. 4. In yet another embodiment spokes 44 may be arcuate, pointing in the proximal direction, rather than straight as shown in Fig. 4.

[0056] Anchor 40 is comprised of a physiologically acceptable metal such as nitinol or stainless steel and, after compression, expands to form an umbrella-like shape. In another embodiment, anchor 40 preferably is comprised of a degradable or

non-degradable polymer such as polypropylene and, after compression, expands to form an umbrella-like shape.

[0057] In the embodiment of the invention shown in Figure 5, a partially cylindrical device 48 comprises a cylindrical portion 50 and a goblet- or mushroom-shaped distal portion 52. In one embodiment, the mushroom-shaped distal portion 52. can also be cylindrical in shape. In another embodiment, the mushroom-shaped distal portion 52 can also be partially spherical in shape or any other suitable shape that has at least one transverse dimension larger than the diameter of the cylindrical portion 50. In general, the diameter or the largest transverse dimensions of the distal portion 52 is greater than the diameter of the cylindrical portion 50. Optionally, cylindrical portion 50 has ridges or projections 54 that aid in fixedly positioning device 48 in an annular fissure, especially at the inner portion of the fissure. Optionally device 48 has a lumen 56 to facilitate positioning device 48 over a stylet or wire (not shown).

[0058] The embodiment of the invention shown in Figures 6 and 7 is an at least partially cylindrical member 64 that comprises a cylindrical member 66 and a distal semi-spherical portion 68 that comprises distally extending projections 70. Preferably projections 70 comprise spaghetti-like shapes suitable for cell propagation.

[0059] Fig. 8 represents an embodiment of the invention where anchor 74 has one or more crossmembers 76 that have projections 78, intended to engage annular tissue 80. Crossmember 76 can have integral projections 78, so that the crossmember 76 and a projection 78 are inserted, preferably at an angle, into anchor 74 prior to delivery, where preferably projection 78 collapses slightly to permit insertion. Alternatively, projections 78 are attached by glue, "fit", or other suitable fixtation after crossmember 76 is positioned within anchor 74. As is shown in the uncompressed anchor 82 depicted in Fig. 9, there could be two or more sets of crossmembers 84 and projections 86.

[0060] In Fig. 10 an anchor 94 is shown in uncompressed condition with a mushroom-shaped distal tip portion 96 and a cylindrical portion 98. Cylindrical portion 98 has radially-extending projections or prongs 102. As shown in the cross-sectional view of Fig. 11, anchor 94 has six projections 102. However, there could be from 2 to as many as 16 or more projections 102, preferably from about 4 to 12. Optionally there could be projections 102 on more than one plane of cylindrical portion 98, preferably 2 or 3 planes altogether, such as proximal neck and/or mid-shaft and/or distal shaft.

[0061] Delivery of anchor 94 is shown in Figs. 12 to 14. Anchor 94 in a compressed state is preloaded into a rigid or substantially rigid tubular member 104. Projections 102 fold around cylindrical portion 98, and the distal portion 106 of a pushing rod or member 108 is positioned adjacent to the proximal surface 110 of cylindrical portion 98. The distal tip 114 of tubular member 104 is positioned in or adjacent to an opening 116 in annulus 120.

[0062] As shown in Figs. 13 and 14, pushing member 108 pushes anchor 94 distally so that anchor 92 fills and engages opening 116. Anchor distal portion 96 expends into the cavity 122 of annulus 120 and seals opening 116. Projections 102 are designed so that tubular member 104 can be rotated or twisted to cause projections 102 to expand into the tissue of annulus 120 to secure anchor 94 in position. When tubular member 104 is withdrawn from opening 116, the bottom portion 124 of cylindrical member 98 fills out the remainder of opening 116. It is within the scope of the invention that when anchor 92 is twisted or rotated in the opposite direction, projections 102 will disengage so that anchor 92 could be revived or repositioned. It is also within the scope of the invention that an anchor can be held, maintained, or retained in position by other retaining means, such as sutures, staples, clips, or the like.

[0063] The material for the attachment device can be degradable or non-degradable materials or fiber-reinforced composites using degradable or non-

degradable materials. The list of non-degradable materials for attachment device include polypropylene, polyethylene, polyethylene terepthalate (PET), Nylon 6, Nylon 6-6, poly imide, polyether imide, PEEK, or their mixtures and copolymers thereof. Aditionally, the list of non-degradable materials for attachment devices includes Teflon, ceramics, stainless steel, platinum or nitinol. The list of degradable materials for attachment device include polymers such as polyglycolic acid ("PGA"), polylactic acid ("PLA"), polycaprolactic acid ("PCL"), poly-p-dioxanone ("PDO"), PGA/PLA copolymers, PGA/PCL copolymers, PGA/PDO copolymers, PLA/PCL copolymers, or their mixtures and copolymers thereof, PLA/PDO copolymers, PCL/PDO copolymers or combinations of any two or more of the foregoing.

[0064] The inventive implantable device is reticulated, i.e., comprises an interconnected network of pores and channels and voids that provides fluid permeability throughout the implantable device and permits cellular and tissue ingrowth and proliferation into the interior of the implantable device. The inventive implantable device is reticulated, i.e., comprises an interconnected and/or inter-communicating network of pores and channels and voids that provides fluid permeability throughout the implantable device and permits cellular and tissue ingrowth and proliferation into the interior of the implantable device. The inventive implantable device is reticulated, i.e., comprises an interconnected and/or inter-communicating network of pores and/or voids and/or channels that provides fluid permeability throughout the implantable device and permits cellular and tissue ingrowth and proliferation into the interior of the implantable device. The biodurable elastomeric matrix or material is considered to be reticulated because its microstructure or the interior structure comprises inter-connected and inter-communicating pores and/or voids bounded by configuration of the struts and intersections that constitute the solid structure. The continuous interconnected void phase is the principle feature of a reticulated structure.

[0065] Preferred scaffold materials for the implants have a reticulated structure with sufficient and required liquid permeability and thus selected to permit blood, or other appropriate bodily fluid, and cells and tissues to access interior surfaces of the implants. This happens due to the presence of inter-connected and inter-communicating, reticulated open pores and/or voids and/or channels that form fluid passageways or fluid permeability providing fluid access all through.

[0066] Preferred materials are at least partially hydrophobic reticulated, elastomeric polymeric matrix for fabricating implants according to the invention are flexible and resilient in recovery, so that the implants are also compressible materials enabling the implants to be compressed and, once the compressive force is released, to then recover to, or toward, substantially or fully to their original size and shape. For example, an implant can be compressed from a relaxed configuration or a size and shape to a compressed size and shape under ambient conditions, e.g., at 25°C to fit into the introducer instrument for insertion into the target orthopedic repair or regeneration site. Alternatively, an implant may be supplied to the medical practitioner performing the implantation operation, in a compressed configuration, for example, contained in a package, preferably a sterile package. The resiliency of the reticulated elastomeric matrix that is used to fabricate the implant causes it to recover to a working size and configuration in situ, at the implantation site, after being released from its compressed state within the introducer instrument. The working size and shape or configuration can be substantially similar to original size and shape after the in situ recovery. In one embodiment, the working size and shape or configuration can be the original size and shape after the in situ recovery. In another embodiment, the implant can be delivered in an uncompressed original size and shape by the introducer instrument.

[0067] Preferred scaffolds are reticulated elastomeric polymeric materials having sufficient structural integrity and durability to endure the intended biological environment, for the intended period of implantation. For structure and durability, at

least partially hydrophobic polymeric scaffold materials are preferred although other materials may be employed if they meet the requirements described herein. Useful materials are preferably elastomeric in that they can be compressed and can resiliently recover to substantially or completely to the pre-compression state. In one embodiment, the implant can be delivered in an uncompressed original size and shape by the introducer instrument. In one embodiment once delivered to the target site, the material can stay anchored at the delivery site under compression with or without exerting significant stress to the neighboring tissues. Alternative reticulated polymeric materials with interconnected pores or networks of pores that permit biological fluids to have ready access throughout the interior of an implant may be employed, for example, woven or nonwoven fabrics or networked composites of microstructural elements of various forms.

[0068] A partially hydrophobic scaffold is preferably constructed of a material selected to be sufficiently biodurable, for the intended period of implantation that the implant will not lose its structural integrity during the implantation time in a biological environment. The biodurable elastomeric matrices forming the scaffold do not exhibit significant symptoms of breakdown, degradation, erosion or significant deterioration of mechanical properties relevant to their use when exposed to biological environments and/or bodily stresses for periods of time commensurate with the use of the implantable device. In one embodiment, the desired period of exposure is to be understood to be at least 29 days, preferably several weeks and most preferably 2 to 5 years or more. This measure is intended to avoid scaffold materials that may decompose or degrade into fragments, for example, fragments that could have undesirable effects such as causing an unwanted tissue response.

[0069] The void phase, preferably continuous and interconnected, of the reticulated polymeric matrix that is used to fabricate the implant of this invention may comprise as little as 50% by volume of the reticulated elastomeric matrix, referring to the volume provided by the interstitial spaces of reticulated elastomeric matrix before

any optional interior pore surface coating or layering is applied. In one embodiment, the volume of void phase as just defined, is from about 70% to about 99% of the volume of reticulated elastomeric matrix. In another embodiment, the volume of void phase as just defined, is from about 70% to about 88% of the volume of reticulated elastomeric matrix. In another embodiment, the volume of void phase is from about 80% to about 88 % of the volume of reticulated elastomeric matrix. In another embodiment, the volume of void phase is from about 80% to about 98% of the volume of reticulated elastomeric matrix. In another embodiment, the volume of void phase is from about 90% to about 98% of the volume of reticulated elastomeric matrix.

[0070] As used herein, when a pore is spherical or substantially spherical, its largest transverse dimension is equivalent to the diameter of the pore. When a pore is non-spherical, for example, ellipsoidal or tetrahedral, its largest transverse dimension is equivalent to the greatest distance within the pore from one pore surface to another, e.g., the major axis length for an ellipsoidal pore or the length of the longest side for a tetrahedral pore. For those skilled in the art, one can routinely estimate the pore frequency from the average cell diameter in microns.

[0071] In one embodiment relating to orthopedic and spinal implant applications and the like, to encourage cellular ingrowth and proliferation and to provide adequate fluid permeability, the average diameter or other largest transverse dimension of pores is at least about 20 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is at least about 50 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is at least about 100 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is at least about 150 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is at least about 250 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is greater than about 250 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is greater than 250

μm. In another embodiment, the average diameter or other largest transverse dimension of pores is at least about 275 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is greater than about 275 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is greater than 275 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is at least about 300 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is greater than about 300 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is greater than 300 μm.

[0072] In another embodiment relating to orthopedic and spinal implant applications and the like, the average diameter or other largest transverse dimension of pores is not greater than about 900 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is not greater than about 750 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is not greater than about 500 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is not greater than about 400 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is not greater than about 300 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is not greater than about 200 μm. In another embodiment, the average diameter or other largest transverse dimension of pores is not greater than about 100 μm.

[0073] In one embodiment, the invention comprises an implantable device having sufficient resilient compressibility to be delivered by a "delivery-device", i.e., a device with a chamber for containing an reticulated elastomeric biodurable reticulated implantable device while it is delivered to the desired site then released at the site, e.g., using a trocar, cannula, or through an endoscopic instrument such as an arthroscope, laproscope, or cystoscope. In another embodiment, the thus-delivered elastomeric biodurable reticulated implantable device substantially regains its shape

after delivery to a biological site and has adequate biodurability and biocompatibility characteristics to be suitable for long-term implantation.

[0074] One embodiment for use in the practice of the invention is a reticulated elastomeric implant which is sufficiently flexible and resilient, i.e., resiliently-compressible, to enable it to be initially compressed under ambient conditions, e.g., at 25°C, from a relaxed configuration to a first, compact configuration for delivery via a delivery-device, e.g., an endoscopic instrument such as an arthroscope, laproscope, cystoscope, or endoscope, or other suitable introducer instrument such as syringe, trocar, etc., for delivery *in vitro* and, thereafter, to expand to a second, working configuration *in situ*. In another embodiment, reticulated elastomeric implant is delivered in an uncompressed state via a delivery-device. Furthermore, in another embodiment, an reticulated elastomeric matrix has the herein described resilient-compressibility after being compressed about 5-95% of an original dimension (e.g., compressed about 19/20th - 1/20th of an original dimension). In another embodiment, an reticulated elastomeric matrix has the herein described resilient-compressibility after being compressed about 10-90% of an original dimension (e.g., compressed about 9/10th - 1/10th of an original dimension). As used herein, reticulated elastomeric implant has "resilient-compressibility", i.e., is "resiliently-compressible", when the second, working configuration, *in vitro*, is at least about 50% of the size of the relaxed configuration in at least one dimension. In another embodiment, the resilient-compressibility of reticulated elastomeric implant is such that the second, working configuration, *in vitro*, is at least about 80% of the size of the relaxed configuration in at least one dimension. In another embodiment, the resilient-compressibility of reticulated elastomeric implant is such that the second, working configuration, *in vitro*, is at least about 90% of the size of the relaxed configuration in at least one dimension. In another embodiment, the resilient-compressibility of reticulated elastomeric implant is such that the second, working configuration, *in vitro*, is at least about 97% of the size of the relaxed configuration in at least one dimension.

[0075] In another embodiment, a reticulated elastomeric matrix has the herein described resilient-compressibility after being compressed about 5-95% of its original volume (e.g., compressed about 19/20th - 1/20th of its original volume). In another embodiment, an reticulated elastomeric matrix has the herein described resilient-compressibility after being compressed about 10-90% of its original volume (e.g., compressed about 9/10th - 1/10th of its original volume). As used herein, "volume" is the volume swept-out by the outermost three-dimensional contour of the reticulated elastomeric matrix. In another embodiment, the resilient-compressibility of reticulated elastomeric implant is such that the second, working configuration, *in vivo*, is at least about 40% of the volume occupied by the relaxed configuration. In another embodiment, the resilient-compressibility of reticulated elastomeric implant is such that the second, working configuration, *in vivo*, is at least about 75 % of the volume occupied by the relaxed configuration. In another embodiment, the resilient-compressibility of reticulated elastomeric implant is such that the second, working configuration, *in vivo*, is at least about 90% of the volume occupied by the relaxed configuration. In another embodiment, the resilient-compressibility of reticulated elastomeric implant is such that the second, working configuration, *in vivo*, occupies at least about 97% of the volume occupied by the reticulated elastomeric matrix in its relaxed configuration.

[0076] In another embodiment, a reticulated elastomeric matrix has the herein described resilient-compressibility is delivered to the target orthopedic or spinal implant but is not compressed during delivery to the target defect site. In another embodiment, after being delivered in an uncompressed state, the resilient-compressibility of reticulated elastomeric implant is such that the second working configuration, *in vivo*, occupies at least about 25% to at least about 40% of the of volume occupied by the reticulated elastomeric matrix in its relaxed configuration. In another embodiment, after being delivered in an uncompressed state, the resilient-compressibility of reticulated elastomeric implant is such that the second working configuration, *in vivo*, occupies at least about 40% to at least about 80% of the of

volume occupied by the reticulated elastomeric matrix in its relaxed configuration. In another embodiment, after being delivered in an uncompressed state, the resilient-compressibility of reticulated elastomeric implant is such that the second working configuration, *in vivo*, occupies at least about 80% to at least about 95% of the of volume occupied by the reticulated elastomeric matrix in its relaxed configuration. In another embodiment, after being delivered in an uncompressed state, the resilient-compressibility of reticulated elastomeric implant is such that the second working configuration, *in vivo*, occupies at least about 95% to at least about 98% of the of volume occupied by the reticulated elastomeric matrix in its relaxed configuration. In another embodiment, after being delivered in an uncompressed state, the resilient-compressibility of reticulated elastomeric implant is such that the second working configuration, *in vivo*, occupies the entire volume occupied by the reticulated elastomeric matrix in its relaxed configuration.

[0077] It is contemplated, in another embodiment, that upon implantation, before their pores become filled with biological fluids, bodily fluids and/or tissue, such implantable devices for orthopedic applications and the like do not entirely fill, cover or span the biological site in which they reside and that an individual implanted reticulated elastomeric matrix will, in many cases although not necessarily, have at least one dimension of no more than 75% of the biological site within the entrance thereto or over 75% of the damaged tissue that is being repaired or replaced. In another embodiment, an individual implanted reticulated elastomeric matrix as described above will have at least one dimension of no more than 95% of the biological site within the entrance thereto or over 95% of the damaged tissue that is being repaired or replaced.

[0078] In another embodiment, that upon implantation, before their pores become filled with biological fluids, bodily fluids and/or tissue, such implantable devices for orthopedic applications and the like substantially fill, cover or span the biological site in which they reside and an individual implanted reticulated

elastomeric matrix will, in many cases, although not necessarily, have at least one dimension of no more than about 98% of the biological site within the entrance thereto or cover 98% of the damaged tissue that is being repaired or replaced. In another embodiment, an individual implanted reticulated elastomeric matrix as described above will have at least one dimension of no more than about 100% of the biological site within the entrance thereto or cover 100% of the damaged tissue that is being repaired or replaced. In another embodiment, an individual implanted reticulated elastomeric matrix as described above will have at least one dimension of no more than about 102% of the biological site within the entrance thereto or cover 102% of the damaged tissue that is being repaired or replaced.

[0079] In another embodiment, that upon implantation, before their pores become filled with biological fluids, bodily fluids and/or tissue, such implantable devices for orthopedic applications and the like overfill, cover or span the biological site in which they reside and an individual implanted reticulated elastomeric matrix will, in many cases, although not necessarily, have at least one dimension of more than about 125% of the biological site within the entrance thereto or cover 125% of the damaged tissue that is being repaired or replaced. In another embodiment, an individual implanted reticulated elastomeric matrix as described above will have at least one dimension of more than about 200% of the biological site within the entrance thereto or cover 200% of the damaged tissue that is being repaired or replaced. In another embodiment, an individual implanted reticulated elastomeric matrix as described above will have at least one dimension of more than about 150% of the biological site within the entrance thereto or cover 150% of the damaged tissue that is being repaired or replaced. In another embodiment, an individual implanted reticulated elastomeric matrix as described above will have at least one dimension of more than about 200% of the biological site within the entrance thereto or cover 200% of the damaged tissue that is being repaired or replaced. In another embodiment, an individual implanted reticulated elastomeric matrix as described above will have at least one dimension of more than about 300% of the biological site within the entrance

thereto or cover 300% of the damaged tissue that is being repaired or replaced.

[0080] Without being bound by any particular theory, it is believed that the absence or substantial absence of cell walls in reticulated implants when compressed to very high degree will allow them to demonstrate resilient recovery in somewhat shorter time (such as recovery time of under 45 seconds when compressed to 75% of their relaxed configuration for 10 minutes and recovery time of under 60 seconds when compressed to 90% of their relaxed configuration for 10 minutes) as compared to un-reticulated porous foams.

[0081] In one embodiment, the reticulated elastomeric matrix has sufficient structural integrity to be self-supporting and free-standing *in vitro*. However, in another embodiment, the elastomeric matrix can be furnished with structural supports such as ribs or struts.

[0082] The reticulated elastomeric matrix useful according to the invention should have sufficient tensile and compressive properties such that it can withstand normal manual or mechanical handling during its intended application and during post-processing steps that may be required or desired without tearing, breaking, crumbling, fragmenting or otherwise disintegrating, shedding pieces or particles, or otherwise losing its structural integrity. The tensile and compressive properties of the matrix material(s) should not be so high as to interfere with the fabrication or other processing of the reticulated elastomeric matrix. The tensile and compressive properties should be appropriate so that they can withstand the forces, loads, deformations and moments experienced by the implant when placed at the target orthopedic or spinal implant site. In one embodiment, the reticulated polymeric matrix that is used to fabricate the implants of this invention has any suitable bulk density, also known as specific gravity, consistent with its other properties. For example, in one embodiment, the bulk density may be from about 0.005 to about 0.15 g/cc (from about 0.31 to about 9.4 lb/ft^3), preferably from about 0.015 to about 0.115 g/cc (from about 0.93 to about 7.2 lb/ft^3) and most preferably from about 0.024 to

about 0.104 g/cc (from about 1.5 to about 6.5 lb/ft^3).

[0083] The reticulated elastomeric matrix has sufficient tensile strength such that it can withstand normal manual or mechanical handling during its intended application and during post-processing steps that may be required or desired without tearing, breaking, crumbling, fragmenting or otherwise disintegrating, shedding pieces or particles, or otherwise losing its structural integrity. The tensile strength of the starting material(s) should not be so high as to interfere with the fabrication or other processing of elastomeric matrix. Thus, for example, in one embodiment, the reticulated polymeric matrix that is used to fabricate the implants of this invention may have a tensile strength of from about 700 to about 70,000 kg/m^2 (from about 1 to about 100 psi). In another embodiment, elastomeric matrix may have a tensile strength of from about 7000 to about 52,500 kg/m^2 (from about 10 to about 75 psi). In another embodiment, elastomeric matrix may have a tensile strength of from about 1,400 to about 14,000 kg/m^2 (from about 2 to about 20 psi) at 20 % ultimate tensile elongation strain. Sufficient ultimate tensile elongation is also desirable. For example, in another embodiment, reticulated elastomeric matrix has an ultimate tensile elongation of at least about 50% to at least about 500%. In yet another embodiment, reticulated elastomeric matrix has an ultimate tensile elongation of at least 75% to at least about 300%.

[0084] In one embodiment, reticulated elastomeric matrix that is used to fabricate the implants of this invention has a compressive strength of from about 700 to about 70,000 kg/m^2 (from about 1 to about 100 psi) at 50% compression strain. In another embodiment, reticulated elastomeric matrix has a compressive strength of from about 1,400 to about 105,000 kg/m^2 (from about 2 to about 150 psi) at 75% compression strain.

[0085] In another embodiment, reticulated elastomeric matrix that is used to fabricate the implants of this invention has a compression set, when compressed to 50% of its thickness at about 25°C, of not more than about 30%. In another

embodiment, reticulated elastomeric matrix has a compression set of not more than about 20%. In another embodiment, reticulated elastomeric matrix has a compression set of not more than about 10%. In another embodiment, reticulated elastomeric matrix has a compression set of not more than about 5%.

[0086] In another embodiment, reticulated elastomeric matrix that is used to fabricate the implants of this invention has a tear strength, of from about 0.18 to about 3.6 kg/linear cm (from about 1 to about 20 lbs/linear inch).

[0087] In another embodiment of the invention the reticulated elastomeric matrix that is used to fabricate the implant can be readily permeable to liquids, permitting flow of liquids, including blood, through the composite device of the invention. The water permeability of the reticulated elastomeric matrix is from about 30 l/min./psi/cm^2 to about 500 l/min./psi/cm^2, preferably from about 50 l/min./psi/cm^2 to about 300 l/min./psi/cm^2. In contrast, permeability of the unreticulated elastomeric matrix is below about 1 1/min./psi/cm^2. In another embodiment, the permeability of the unretriculated elastomeric amtrix is below about 5 1/min./psi/cm^2.

[0088] In general, suitable biodurable reticulated elastomeric partially hydrophobic polymeric matrix that is used to fabricate the implant of this invention or for use as scaffold material for the implant in the practice of the present invention, in one embodiment sufficiently well characterized, comprise elastomers that have or can be formulated with the desirable mechanical properties described in the present specification and have a chemistry favorable to biodurability such that they provide a reasonable expectation of adequate biodurability.

[0089] Various biodurable reticulated hydrophobic polyurethane materials are suitable for this purpose. In one embodiment, structural materials for the inventive reticulated elastomers are synthetic polymers, especially, but not exclusively, elastomeric polymers that are resistant to biological degradation, for example, polycarbonate polyurethane-urea, polycarbonate polyurea-urethane, polycarbonate

polyurethane, polycarbonate polysiloxane polyurethane, and polysiloxane polyurethane, and the like. Such elastomers are generally hydrophobic but, pursuant to the invention, may be treated to have surfaces that are less hydrophobic or somewhat hydrophilic. In another embodiment, such elastomers may be produced with surfaces that are less hydrophobic or somewhat hydrophilic.

[0090] The invention can employ, for implanting, a biodurable reticulatable elastomeric partially hydrophobic polymeric scaffold material or matrix for fabricating the implant or a material. More particularly, in one embodiment, the invention provides a biodurable elastomeric polyurethane scaffold material or matrix which is made by synthesizing the scaffold material or matrix preferably from a polycarbonate polyol component and an isocyanate component by polymerization, cross-linking and foaming, thereby forming pores, followed by reticulation of the porous material to provide a biodurable reticulated elastomeric product with inter-connected and/or inter-communicating pores and channels. The product is designated as a polycarbonate polyurethane, being a polymer comprising urethane groups formed from, e.g., the hydroxyl groups of the polycarbonate polyol component and the isocyanate groups of the isocyanate component. In another embodiment, the invention provides a biodurable elastomeric polyurethane scaffold material or matrix which is made by synthesizing the scaffold material or matrix preferably from a polycarbonate polyol component and an isocyanate component by polymerization, cross-linking and foaming, thereby forming pores, and using water as a blowing agent and/or foaming agent during the synthesis, followed by reticulation of the porous material to provide a biodurable reticulated elastomeric product with inter-connected and/or inter-communicating pores and channels. This product is designated as a polycarbonate polyurethane-urea or polycarbonate polyurea-urethane, being a polymer comprising urethane groups formed from, e.g., the hydroxyl groups of the polycarbonate polyol component and the isocyanate groups of the isocyanate component and also comprising urea groups formed from reaction of water with the isocyanate groups. In all of these embodiments, the process employs controlled

chemistry to provide a reticulated elastomeric matrix or product with good biodurability characteristics. The matrix or product employing chemistry that avoids biologically undesirable or nocuous constituents therein.

[0091] In one embodiment, the starting material for synthesizing the biodurable reticulated elastomeric partially hydrophobic polymeric matrix contains at least one polyol component to provide the so-called soft segement. For the purposes of this application, the term "polyol component" includes molecules comprising, on the average, about 2 hydroxyl groups per molecule, i.e., a difunctional polyol or a diol, as well as those molecules comprising, on the average, greater than about 2 hydroxyl groups per molecule, i.e., a polyol or a multi-functional polyol. In one embodiment, this soft segment polyol is terminated with hydroxyl groups, either primary or secondary. Exemplary polyols can comprise, on the average, from about 2 to about 5 hydroxyl groups per molecule. In one embodiment, as one starting material, the process employs a difunctional polyol component in which the hydroxyl group functionality of the diol is about 2. In another embodiment, the soft segment is composed of a polyol component that is generally of a relatively low molecular weight, typically from about 500 to about 6,000 daltons and preferably between 1000 to 2500 daltons. Examples of suitable polyol components include but not limited to polycarbonate polyol, hydrocarbon polyol, polysiloxane polyol, poly(carbonate-co-hydrocarbon) polyol, poly(carbonate-co-siloxane) polyol, poly(hydrocarbon-co-siloxane) polyol, polysiloxane polyol and copolymers and mixtures thereof.

[0092] In one embodiment, the starting material for synthesizing the biodurable reticulated elastomeric partially hydrophobic polymeric matrix contains at least one isocyanate component and, optionally, at least one chain extender component to provide the so-called "hard segment". In one embodiment, the starting material for synthesizing the biodurable reticulated elastomeric partially hydrophobic polymeric matrix contains at least one isocyanate component. For the purposes of this application, the term "isocyanate component" includes molecules comprising, on the

average, about 2 isocyanate groups per molecule as well as those molecules comprising, on the average, greater than about 2 isocyanate groups per molecule. The isocyanate groups of the isocyanate component are reactive with reactive hydrogen groups of the other ingredients, e.g., with hydrogen bonded to oxygen in hydroxyl groups of the polyol component, with hydrogen bonded to nitrogen in amine groups, chain extender, crosslinker and/or water. In one embodiment, the average number of isocyanate groups per molecule in the isocyanate component is about 2. In another embodiment, the average number of isocyanate groups per molecule in the isocyanate component is greater than about 2.

[0093] The isocyanate index, a quantity well known to those in the art, is the mole ratio of the number of isocyanate groups in a formulation available for reaction to the number of groups in the formulation that are able to react with those isocyanate groups, e.g., the reactive groups of diol(s), polyol component(s), chain extender(s) and water, when present. In one embodiment, the isocyanate index is from about 0.9 to about 1.1. In another embodiment, the isocyanate index is from about 0.9 to about 1.02. In another embodiment, the isocyanate index is from about 0.98 to about 1.02. In another embodiment, the isocyanate index is from about 0.9 to about 1.0. In another embodiment, the isocyanate index is from about 0.9 to about 0.98.

[0094] In one embodiment, a small quantity of an optional ingredient, such as a multi-functional hydroxyl compound or other cross-linker having a functionality greater than 2, is present to allow crosslinking and/or to achieve a stable foam, i.e., a foam that does not collapse to become non-foamlike. Alternatively, or in addition, polyfunctional adducts of aliphatic and cycloaliphatic isocyanates can be used to impart cross-linking in combination with aromatic diisocyanates. Alternatively, or in addition, polyfunctional adducts of aliphatic and cycloaliphatic isocyanates can be used to impart cross-linking in combination with aliphatic diisocyanates. Alternatively, or in addition, polymeric aromatic diisocyanates can be used to impart cross-linking. The presence of these components and adducts with functionality

higher than 2 in the hard segment component allows for cross-linking to occur. In distinction to the cross-linking described above which is termed chemical cross-linking, additional cross-linking arises out of hydrogen bonding in and between both the hard and soft phases of the matrix and is termed as physical cross-linking.

[0095] Exemplary diisocyanates include aliphatic diisocyanates, isocyanates comprising aromatic groups, the so-called "aromatic diisocyanates", and mixtures thereof. Aliphatic diisocyanates include tetramethylene diisocyanate, cyclohexane-1,2-diisocyanate, cyclohexane-1,4-diisocyanate, hexamethylene diisocyanate, isophorone diisocyanate, methylene-bis-(p-cyclohexyl isocyanate) ("H12 MDI"), and mixtures thereof. Aromatic diisocyanates include p-phenylene diisocyanate, 4,4'-diphenylmethane diisocyanate ("4,4'-MDI"), 2,4'-diphenylmethane diisocyanate ("2,4'-MDI"), polymeric MDI, and mixtures thereof. Examples of optional chain extenders include diols, diamines, alkanol amines or a mixture thereof.

[0096] In one embodiment, the starting material for synthesizing the biodurable reticulated elastomeric partially hydrophobic polymeric matrix contains at least one blowing agent such as water. Other exemplary blowing agents include the physical blowing agents, e.g., volatile organic chemicals such as hydrocarbons, ethanol and acetone, and various fluorocarbons, hydrofluorocarbons, chlorofluorocarbons, and hydrochlorofluorocarbons. Additional exemplary blowing agents include the physical blowing agents such as gases as nitrogen, helium, etc., that can additionally act as nucleating agent and whose amount and the pressure under which they are introduced during matrix formation can be used to control the density of the biodurable, elastomeric and partially hydrophobic polymeric matrix. In one embodiment, the hard segments also contain a urea component formed during foaming reaction with water. In one embodiment, the reaction of water with an isocyanate group yields carbon dioxide, which serves as a blowing agent. The amount of blowing agent, e.g., water, is adjusted to obtain different densities of non-reticulated foams. A reduced amount

of blowing agent such as water may reduce the number of urea linkages in the material.

[0097] In another embodiment, any or all of the processing approaches of the invention may be used to make foam with a density greater than 3.4 lbs/ft^3 (0.054 g/cc). In this embodiment, optionally some amount of crosslinker(s), such as glycerol, are used; the functionality of the isocyanate component is from 2.0 to 2.5; the isocyanate component consists essentially of 4, 4 diphenylmethane diisocyanate ("4,4'-MDI"), and the remaining components being 2,4'-diphenylmethane diisocyanate ("2,4'-MDI"), polymeric MDI; and the amount of 4,4'-MDI is greater than about 55% by weight of the isocyanate component. It may also include additional amount of 4,4'-MDI. The molecular weight of the polyol component is from about 500 to 3000 Daltons but preferably between 1,000 to about 2,000 Daltons. The amount of blowing agent, e.g., water, is adjusted to obtain non-reticulated foam with densities greater than 3.4 lbs/ft^3 (0.054 g/cc). A reduced amount of blowing agent may reduce the number of urea linkages in the material. In one embodiment, any reduction in stiffness and/or tensile strength and/or compressive strength caused by fewer urea linkages and/or by lower crosslinking can be compensated for by using di-functional chain extenders, such as butanediol, and/or increasing the density of the foam. In another embodiment, any reduction in stiffness and/or tensile strength and/or compressive strength caused by fewer urea linkages and/or lower crosslinking can be compensated for by using or increasing the amount or proportion of 4,4'-MDI of the isocyanate component. Although not bound by any particular theory, it is believed that by controlling the degree of cross-linking in the hard phase, amount of 4,4 MDI and by controlling density of the foam material, it is possible to increase the foam's toughness and/or elongation to break. This consequently should allow for more efficient reticulation because the higher density, higher amount of 4,4 MDI and lighter cross-linking results in tougher matrix material which can better withstand the sudden impact a reticulation process can provide with minimal, if any, damage to struts.

[0098] In one embodiment, implantable device can be rendered radiopaque to facilitate *in vivo* imaging, for example, by adhering to, covalently bonding to and/or incorporating into the elastomeric matrix itself particles of a radio-opaque material. Radio-opaque materials include titanium, tantalum, tungsten, barium sulfate or other suitable material known to those skilled in the art.

[0099] In one embodiment, the starting material of the biodurable reticulated elastomeric partially hydrophobic polymeric matrix is a commercial polyurethane polymers are linear, not crosslinked, polymers, therefore, they are soluble, can be melted, readily analyzable and readily characterizable. In this embodiment, the starting polymer provides good biodurability characteristics. The reticulated elastomeric matrix is produced by taking a solution of the commercial polymer such as polyurethane and charging it into a mold that has been fabricated with surfaces defining a microstructural configuration for the final implant or scaffold, solidifying the polymeric material and removing the sacrificial mold by melting, dissolving or subliming-away the sacrificial mold. In one embodiment, the solvents can be lyophilized leaving at least a partially or fully reticulated material matrix. The matrix or product employing a foaming process that avoids biologically undesirable or nocuous constituents therein.

[00100] Of particular interest are thermoplastic elastomers such as polyurethanes whose chemistry is associated with good biodurability properties, for example. In one embodiment, such thermoplastic polyurethane elastomers include polycarbonate polyurethanes, polysiloxane polyurethanes, polyurethanes with so-called "mixed" soft segments, and mixtures thereof. Mixed soft segment polyurethanes are known to those skilled in the art and include, e.g., polycarbonate-polysiloxane polyurethanes. In another embodiment, the thermoplastic polyurethane elastomer comprises at least one diisocyanate in the isocyanate component, at least one chain extender and at least one diol, and may be formed from any combination of the diisocyanates, difunctional chain extenders and diols described in detail above. Some suitable thermoplastic

polyurethanes for practicing the invention, in one embodiment suitably characterized as described herein, include: polyurethanes with mixed soft segments comprising polysiloxane together with a polycarbonate component.

[00101] In one embodiment, the weight average molecular weight of the thermoplastic elastomer is from about 30,000 to about 500,000 Daltons. In another embodiment, the weight average molecular weight of the thermoplastic elastomer is from about 50,000 to about 250,000 Daltons.

[00102] Some commercially-available thermoplastic elastomers suitable for use in practicing the present invention include the line of polycarbonate polyurethanes supplied under the trademark BIONATE® by The Polymer Technology Group Inc. (Berkeley, CA). For example, the very well-characterized grades of polycarbonate polyurethane polymer BIONATE® 80A, 55 and 90 are soluble in THF, DMF, DMAT, DMSO, or a mixture of two or more thereof, processable, reportedly have good mechanical properties, lack cytotoxicity, lack mutagenicity, lack carcinogenicity and are non-hemolytic. Another commercially-available elastomer suitable for use in practicing the present invention is the CHRONOFLEX® C line of biodurable medical grade polycarbonate aromatic polyurethane thermoplastic elastomers available from CardioTech International, Inc. (Woburn, MA).

[00103] Other possible embodiments of the materials used to fabricate the implants of this invention are described in co-pending, commonly assigned U.S. patent applications Serial No. 10/749,742, filed December 30, 2003, titled "Reticulated Elastomeric Matrices, Their Manufacture and Use in Implantable Devices", Serial No. 10/848,624, filed May 17, 2004, titled "Reticulated Elastomeric Matrices, Their Manufacture and Use In Implantable Devices", and Serial No. 10/990,982, filed July 27, 2004, titled "Endovascular Treatment Devices and Methods", each of which is incorporated herein by reference in its entirety.

[00104] It is within the scope of this invention that the elastomeric scaffold may optionally have a simple dip or spray polymer coating, the coating optionally comprising a pharmaceutically-active agent, such as a therapeutic agent or drug. In one embodiment the coating may be a solution and the polymer content in the coating solution is from about 1% to about 40% by weight. In another embodiment, the polymer content in the coating solution may be from about 1% to about 20% by weight. In another embodiment, the polymer content in the coating solution may be from about 1% to about 10% by weight.

[00105] In one embodiment of the invention, a biodurable reticulated elastomeric matrix has a coating comprising material selected to encourage cellular ingrowth and proliferation. The coating material can, for example, comprise a foamed coating of a biodegradable material, optionally, collagen, fibronectin, elastin, hyaluronic acid and mixtures thereof. Alternatively, the coating comprises a biodegradable polymer and an inorganic component.

[00106] In another embodiment, the reticulated biodurable elastomer is coated or impregnated with a material such as, for example, polyglycolic acid ("PGA"), polylactic acid ("PLA"), polycaprolactic acid ("PCL"), poly-p-dioxanone ("PDO"), PGA/PLA copolymers, PGA/PCL copolymers, PGA/PDO copolymers, PLA/PCL copolymers, PLA/PDO copolymers, PCL/PDO copolymers or combinations of any two or more of the foregoing.

[00107] The solvent or solvent blend for the coating solution is chosen with consideration given to, *inter alia*, the proper balancing the viscosity, deposition level of the polymer, wetting rate and evaporation rate of the solvent to properly coat solid phase as known to those in the art. In one embodiment, the solvent is chosen such the polymer is soluble in the solvent. In another embodiment, the solvent is substantially completely removed from the coating. In another embodiment, the solvent is non-toxic, non-carcinogenic and environmentally benign. Mixed solvent systems can be advantageous for controlling the viscosity and evaporation rates. In all cases, the

solvent should not react with the coating polymer. Solvents include, but are not limited to, acetone, N-methylpyrrolidone ("NMP"), DMSO, toluene, methylene chloride, chloroform, 1,1,2-trichloroethane ("TCE"), various freons, dioxane, ethyl acetate, THF, DMF and DMAC.

[00108] In another embodiment, the film-forming coating polymer is a thermoplastic polymer that is melted, enters the pores of the elastomeric matrix and, upon cooling or solidifying, forms a coating on at least a portion of the solid material of the elastomeric matrix . In another embodiment, the processing temperature of the thermoplastic coating polymer in its melted form is above about 60°C. In another embodiment, the processing temperature of the thermoplastic coating polymer in its melted form is above about 90°C. In another embodiment, the processing temperature of the thermoplastic coating polymer in its melted form is above about 120°C.

[00109] In a further embodiment of the invention, described in more detail below, some or all of the pores of the elastomeric matrix are coated or filled with a cellular ingrowth promoter. In another embodiment, the promoter can be foamed. In another embodiment, the promoter can be present as a film. The promoter can be a biodegradable material to promote cellular invasion of the elastomeric matrix *in vivo*. Promoters include naturally occurring materials that can be enzymatically degraded in the human body or are hydrolytically unstable in the human body, such as fibrin, fibrinogen, collagen, elastin, hyaluronic acid and absorbable biocompatible polysaccharides, such as chitosan, starch, fatty acids (and esters thereof), glucoso-glycans and hyaluronic acid. In some embodiments, the pore surface of the elastomeric matrix is coated or impregnated, as described above, but substituting the promoter for the biocompatible polymer or adding the promoter to the biocompatible polymer, to encourage cellular ingrowth and proliferation.

[00110] In one embodiment, the coating or impregnating process is conducted so as to ensure that the product "composite elastomeric implantable device", i.e., a reticulated elastomeric matrix and a coating, as used herein, retains sufficient

resiliency after compression such that it can be delivery-device delivered, e.g., catheter, syringe or endoscope delivered. Some embodiments of such a composite elastomeric implantable device will now be described with reference to collagen, by way of non-limiting example, with the understanding that other materials may be employed in place of collagen, as described above.

[00111] Collagen may be infiltrated by forcing, e.g., with pressure, an aqueous collagen slurry, suspension or solution into the pores of an elastomeric matrix. The collagen may be Type I, II or III or mixtures thereof. In one embodiment, the collagen type comprises at least 90% collagen I. The concentration of collagen is from about 0.3% to about 2.0% by weight and the pH of the slurry, suspension or solution is adjusted to be from about 2.6 to about 5.0 at the time of lyophilization. Alternatively, collagen may be infiltrated by dipping an elastomeric matrix into a collagen slurry.

[00112] As compared with the uncoated reticulated elastomer, the composite elastomeric implantable device can have a void phase that is slightly reduced in volume. In one embodiment, the composite elastomeric implantable device retains good fluid permeability and sufficient porosity for ingrowth and proliferation of fibroblasts or other cells.

[00113] Optionally, the lyophilized collagen can be crosslinked to control the rate of *in vivo* enzymatic degradation of the collagen coating and to control the ability of the collagen coating to bond to the elastomeric matrix. Without being bound by any particular theory, it is thought that when the composite elastomeric implantable device is implanted, tissue-forming agents that have a high affinity to collagen, such as fibroblasts, will more readily invade the collagen-impregnated elastomeric matrix than the uncoated matrix. It is further thought, again without being bound by any particular theory, that as the collagen enzymatically degrades, new tissue invades and fills voids left by the degrading collagen while also infiltrating and filling other available spaces in the elastomeric matrix. Such a collagen coated or impregnated

elastomeric matrix is thought, without being bound by any particular theory, to be additionally advantageous for the structural integrity provided by the reinforcing effect of the collagen within the pores of the elastomeric matrix which can impart greater rigidity and structural stability to various configurations of the elastomeric matrix .

[00114] The biodurable reticulated elastomeric matrix useful according to this invention can support cell types including cells secreting structural proteins and cells that produce proteins characterizing organ function. The ability of the elastomeric matrix to facilitate the co-existence of multiple cell types together and its ability to support protein secreting cells demonstrates the applicability of the elastomeric matrix in organ growth in vitro or in vivo and in organ reconstruction. In addition, the biodurable reticulated elastomeric matrix may also be used in the scale up of human cell lines for implantation to the body for many applications including implantation of fibroblasts, chondrocytes, osteoblasts, osteoclasts, osteocytes, synovial cells, bone marrow stromal cells, stem cells, fibrocartilage cells, endothelial cells, smooth muscle cells, adipocytes, cardiomyocytes, myocytes, keratinocytes, hepatocytes, leukocytes, macrophages, endocrine cells, genitourinary cells, lymphatic vessel cells, pancreatic islet cells, muscle cells, intestinal cells, kidney cells, blood vessel cells, thyroid cells, parathyroid cells, cells of the adrenal-hypothalamic pituitary axis, bile duct cells, ovarian or testicular cells, salivary secretory cells, renal cells, epithelial cells, nerve cells, stem cells, progenitor cells, myoblasts and intestinal cells.

[00115] New tissue can be obtained through implantation of cells seeded in elastomeric matrices (either prior to or concurrent to or subsequent to implantation). In this case, the elastomeric matrices may be configured either in a closed manner to protect the implanted cells from the body's immune system, or in an open manner so that the new cells can be incorporated into the body. Thus, in another embodiment, the cells may be incorporated, i.e., cultured and proliferated, onto the elastomeric

matrix prior, concurrent or subsequent to implantation of the elastomeric matrix in the patient.

[00116] In one embodiment, the implantable device made from biodurable reticulated elastomeric matrix can be seeded with a type of cell and cultured before being inserted into the patient, optionally using a delivery-device, for the explicit purpose of tissue repair or tissue regeneration. It is necessary to perform the tissue or cell culture in a suitable culture medium with or without stimulus such as stress or orientation. The cells include fibroblasts, chondrocytes, osteoblasts, osteoclasts, osteocytes, synovial cells, bone marrow stromal cells, stem cells, fibrocartilage cells, endothelial cells and smooth muscle cells.

[00117] Surfaces on the biodurable reticulated elastomeric matrix possessing different pore morphology, size, shape and orientation may be cultured with different type of cells to develop cellular tissue engineering implantable devices that are specifically targeted towards orthopedic applications, especially in soft tissue attachment, repair, re-generation, augmentation and/or support encompassing spine, shoulder, knee, hand, joints, and in the growth of a prosthetic organ. In another embodiment, all the surfaces on the biodurable reticulated elastomeric matrix possessing similar pore morphology, size, shape and orientation may be so cultured.

[00118] In another embodiment, the film-forming polymer used to coat the reticulated elastomeric matrix can provide a vehicle for the delivery of and/or the controlled release of a pharmaceutically-active agent, for example, a drug, such as is described in the copending applications. In another embodiment, the pharmaceutically-active agent is admixed with, covalently bonded to and/or adsorbed in or on the coating of the elastomeric matrix to provide a pharmaceutical composition. In another embodiment, the components, polymers and/or blends used to form the foam comprise a pharmaceutically-active agent. To form these foams, the previously described components, polymers and/or blends are admixed with the pharmaceutically-active agent prior to forming the foam or the pharmaceutically-

active agent is loaded into the foam after it is formed.

[00119] In one embodiment, the coating polymer and pharmaceutically-active agent have a common solvent. This can provide a coating that is a solution. In another embodiment, the pharmaceutically-active agent can be present as a solid dispersion in a solution of the coating polymer in a solvent.

[00120] A reticulated elastomeric matrix comprising a pharmaceutically-active agent may be formulated by mixing one or more pharmaceutically-active agent with the polymer used to make the foam, with the solvent or with the polymer-solvent mixture and foamed. Alternatively, a pharmaceutically-active agent can be coated onto the foam, in one embodiment, using a pharmaceutically-acceptable carrier. If melt-coating isemployed, then, in another embodiment, the pharmaceutically-active agent withstands melt processing temperatures without substantial diminution of its efficacy.

[00121] Formulations comprising a pharmaceutically-active agent can be prepared by admixing, covalently bonding and/or adsorbing one or more pharmaceutically-active agents with the coating of the reticulated elastomeric matrix or by incorporating the pharmaceutically-active agent into additional hydrophobic or hydrophilic coatings. The pharmaceutically-active agent may be present as a liquid, a finely divided solid or another appropriate physical form. Typically, but optionally, the matrix can include one or more conventional additives, such as diluents, carriers, excipients, stabilizers and the like.

[00122] In another embodiment, a top coating can be applied to delay release of the pharmaceutically-active agent. In another embodiment, a top coating can be used as the matrix for the delivery of a second pharmaceutically-active agent. A layered coating, comprising respective layers of fast- and slow-hydrolyzing polymer, can be used to stage release of the pharmaceutically-active agent or to control release of different pharmaceutically-active agents placed in the different layers. Polymer

blends may also be used to control the release rate of different pharmaceutically-active agents or to provide a desirable balance of coating characteristics (e.g., elasticity, toughness) and drug delivery characteristics (e.g., release profile). Polymers with differing solvent solubilities can be used to build-up different polymer layers that may be used to deliver different pharmaceutically-active agents or to control the release profile of a pharmaceutically-active agents.

[00123] The amount of pharmaceutically-active agent present depends upon the particular pharmaceutically-active agent employed and medical condition being treated. In one embodiment, the pharmaceutically-active agent is present in an effective amount. In another embodiment, the amount of pharmaceutically-active agent represents from about 0.01% to about 60% of the coating by weight. In another embodiment, the amount of pharmaceutically-active agent represents from about 0.01% to about 40% of the coating by weight. In another embodiment, the amount of pharmaceutically-active agent represents from about 0.1% to about 20% of the coating by weight.

[00124] Many different pharmaceutically-active agents can be used in conjunction with the reticulated elastomeric matrix. In general, pharmaceutically-active agents that may be administered via pharmaceutical compositions of this invention include, without limitation, any therapeutic or pharmaceutically-active agent (including but not limited to nucleic acids, proteins, lipids, and carbohydrates) that possesses desirable physiologic characteristics for application to the implant site or administration via a pharmaceutical compositions of the invention. Therapeutics include, without limitation, antiinfectives such as antibiotics and antiviral agents; chemotherapeutic agents (e.g., anticancer agents); anti-rejection agents; analgesics and analgesic combinations; anti-inflammatory agents; hormones such as steroids; growth factors (including but not limited to cytokines, chemokines, and interleukins) and other naturally derived or genetically engineered proteins, polysaccharides, glycoproteins and lipoproteins. These growth factors are described in The Cellular

and Molecular Basis of Bone Formation and Repair by Vicki Rosen and R. Scott Thies, published by R. G. Landes Company, hereby incorporated herein by reference. Additional therapeutics include thrombin inhibitors, antithrombogenic agents, thrombolytic agents, fibrinolytic agents, vasospasm inhibitors, calcium channel blockers, vasodilators, antihypertensive agents, antimicrobial agents, antibiotics, inhibitors of surface glycoprotein receptors, antiplatelet agents, antimitotics, microtubule inhibitors, anti secretory agents, actin inhibitors, remodeling inhibitors, antisense nucleotides, anti metabolites, antiproliferatives, anticancer chemotherapeutic agents, anti-inflammatory steroids, non-steroidal anti-inflammatory agents, immunosuppressive agents, growth hormone antagonists, growth factors, dopamine agonists, radiotherapeutic agents, peptides, proteins, enzymes, extracellular matrix components, angiotensin-converting enzyme (ACE) inhibitors, free radical scavengers, chelators, antioxidants, anti polymerases, antiviral agents, photodynamic therapy agents and gene therapy agents.

[00125] Additionally, various proteins (including short chain peptides), growth agents, chemotatic agents, growth factor receptors or ceramic particles can be added to the foams during processing, adsorbed onto the surface or back-filled into the foams after the foams are made. For example, in one embodiment, the pores of the foam may be partially or completely filled with biocompatible resorbable synthetic polymers or biopolymers (such as collagen or elastin), biocompatible ceramic materials (such as hydroxyapatite), and combinations thereof, and may optionally contain materials that promote tissue growth through the device. Such tissue-growth materials include but are not limited to autograft, allograft or xenograft bone, bone marrow and morphogenic proteins. Biopolymers can also be used as conductive or chemotactic materials, or as delivery vehicles for growth factors. Examples include recombinant collagen, animal-derived collagen, elastin and hyaluronic acid. Pharmaceutically-active coatings or surface treatments could also be present on the surface of the materials. For example, bioactive peptide sequences (RGD's) could be attached to the surface to facilitate protein adsorption and subsequent cell tissue

attachment. In a further embodiment of the invention, the pores of biodurable reticulated elastomeric matrix that are used to fabricate the implants of this invention are coated or filled with a cellular ingrowth promoter. In another embodiment, the promoter can be foamed. In another embodiment, the promoter can be present as a film. The promoter can be a biodegradable material to promote cellular invasion of pores biodurable reticulated elastomeric matrix that are used to fabricate the implants of this invention in vivo. Promoters include naturally occurring materials that can be enzymatically degraded in the human body or are hydrolytically unstable in the human body, such as fibrin, fibrinogen, collagen, elastin, hyaluronic acid and absorbable biocompatible polysaccharides, such as chitosan, starch, fatty acids (and esters thereof), glucoso-glycans and hyaluronic acid. In some embodiments, the pore surface of the biodurable reticulated elastomeric matrix that are used to fabricate the implants of this invention is coated or impregnated, as described in the previous section but substituting the promoter for the biocompatible polymer or adding the promoter to the biocompatible polymer, to encourage cellular ingrowth and proliferation.

[00126] Bioactive molecules include, without limitation, proteins, collagens (including types IV and XVIII), fibrillar collagens (including types I, II, III, V, XI), FACIT collagens (types IX, XII, XIV), other collagens (types VI, VII, XIII), short chain collagens (types VIII, X), elastin, entactin-1, fibrillin, fibronectin, fibrin, fibrinogen, fibroglycan, fibromodulin, fibulin, glypican, vitronectin, laminin, nidogen, matrilin, perlecan, heparin, heparan sulfate proteoglycans, decorin, filaggrin, keratin, syndecan, agrin, integrins, aggrecan, biglycan, bone sialoprotein, cartilage matrix protein, Cat-301 proteoglycan, CD44, cholinesterase, HB-GAM, hyaluronan, hyaluronan binding proteins, mucins, osteopontin, plasminogen, plasminogen activator inhibitors, restrictin, serglycin, tenascin, thrombospondin, tissue-type plasminogen activator, urokinase type plasminogen activator, versican, von Willebrand factor, dextran, arabinogalactan, chitosan, polyactide-glycolide, alginates, pullulan, gelatin and albumin.

[00127] Additional bioactive molecules include, without limitation, cell adhesion molecules and matricellular proteins, including those of the immunoglobulin (Ig; including monoclonal and polyclonal antibodies), cadherin, integrin, selectin, and H-CAM superfamilies. Examples include, without limitation, AMOG, CD2, CD4, CD8, C-CAM (CELL-CAM 105), cell surface galactosyltransferase, connexins, desmocollins, desmoglein, fasciclins, F11, GP Ib-IX complex, intercellular adhesion molecules, leukocyte common antigen protein tyrosine phosphate (LCA, CD45), LFA- 1, LFA-3, mannose binding proteins (MBP), MTJC18, myelin associated glycoprotein (MAG), neural cell adhesion molecule (NCAM), neurofascin, neruoglian, neurotactin, netrin, PECAM-1, PH-20, semaphorin, TAG-1, VCAM-1, SPARC/osteonectin, CCN1 (CYR61), CCN2 (CTGF; Connective Tissue Growth Factor), CCN3 (NOV), CCN4 (WISP-1), CCN5 (WISP-2), CCN6 (WISP-3), occludin and claudin. Growth factors include, without limitation, BMP's (1-7), BMP-like Proteins (GFD-5, -7, -8), epidermal growth factor (EGF), erythropoietin (EPO), fibroblast growth factor (FGF), growth hormone (GH), growth hormone releasing factor (GHRF), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), insulin, insulin-like growth factors (IGF-I, IGF-II), insulin-like growth factor binding proteins (IGFBP), macrophage colony-stimulating factor (M-CSF), Multi-CSF (II-3), platelet-derived growth factor (PDGF), tumor growth factors (TGF-alpha, TGF-beta), tumor necrosis factor (TNF-alpha), vascular endothelial growth factors (VEGF's), angiopoietins, placenta growth factor (PIGF), interleukins, and receptor proteins or other molecules that are known to bind with the aforementioned factors. Short-chain peptides include, without limitation (designated by single letter amino acid code), RGD, EILDV, RGDS, RGES, RFDS, GRDGS, GRGS, GRGDTP and QPPRARI. One possible material for use in the present invention comprises a resiliently compressible composite polyurethane material comprising a hydrophilic foam coated on and throughout the pore surfaces of a hydrophobic foam scaffold. One suitable such material is the composite foam disclosed in co-pending, commonly assigned U.S. patent applications Serial No.

10/692,055, filed October 22, 2003, Serial No. 10/749,742, filed December 30, 2003, Serial No. 10/848,624, filed May 17, 2004, and Serial No. 10/900,982, filed July 27, 2004, each of which is incorporated herein by reference in its entirety. The hydrophobic foam provides support and resilient compressibility enabling the desired collapsing of the implant for delivery and reconstitution *in situ.*

[00128] The elastomeric matrix useful according to the invention may be molded into any of a wide variety of shapes and sizes during its formation or production. The shape may be a working configuration, such as any of the shapes and configurations described above, or the shape may be for bulk stock. Stock items may subsequently be cut, trimmed, punched or otherwise shaped for end use. The sizing and shaping can be carried out by, for example, using a blade, punch, drill or laser. In each of these embodiments, the processing temperature or temperatures of the cutting tools for shaping and sizing can be greater than about 100°C. In another embodiment, the processing temperature(s) of the cutting tools for shaping and sizing can be greater than about 130°C. Finishing steps can include, in one embodiment, trimming of macrostructural surface protrusions, such as struts or the like, which can irritate biological tissues. In another embodiment, finishing steps can include heat annealing. Annealing can be carried out before or after final cutting and shaping.

[00129] The dimensions of the shaped and sized devices made from the elastomeric matrix can vary depending on the application. In one embodiment, major dimensions of a device, such as device 30 or device 48, prior to being compressed and delivered, are from about 5 mm to about 30 mm in one direction and from about 5mm to about 30 mm in another direction. In another embodiment, major dimensions of a device, such as device 30 or device 48, prior to being compressed and delivered are from about 8 mm to about 25 mm in one direction and from about 8 mm to about 25 mm in another direction. The length of a cylindrical portion of a device, such as device 30 or device 48, according to the invention is expected to be from about 6 mm to about 14 mm, since that is approximately the typical radial thickness of a patient's

annulus. The diameter or the largest transverse dimension of the cylindrical portion of a device, such as cylindrical part 32 or cylindrical part 50, according to the invention is expected to be from about 5 mm to about 30 mm, preferably from about 8 mm to about 20 mm. The diameter or the largest transverse dimension of the partial cylindrical or partial spherical portion of a device, such as expanded portion 34 or mushrrom-shape distal portion 52, according to the invention is expected to be from about 8 mm to about 40 mm, preferably from about 10 mm to about 30 mm. The elastomeric matrix can exhibit compression set upon being compressed and transported through a delivery-device, e.g., a trocar, cannula, or catheter, with assisted visualization. In another embodiment, compression set and its standard deviation are taken into consideration when designing the pre-compression dimensions of the device.

[00130] Biodurable reticulated elastomeric matrices, or an implantable device system comprising such matrices, can be sterilized by any method known to the art including gamma irradiation, autoclaving, ethylene oxide sterilization, infrared irradiation and electron beam irradiation. In one embodiment, biodurable elastomers used to fabricate the elastomeric matrix tolerate such sterilization without loss of useful physical and mechanical properties. The use of gamma irradiation can potentially provide additional crosslinking to enhance the performance of the device.

[00131] In one embodiment, the sterilized products may be packaged in uncompressed state in sterile packages of paper, polymer or other suitable material. In embodiment, the elastomeric matrix remains uncompressed in such a package for typical commercial storage and distribution times, which will commonly exceed 3 months and may be up to 1 or 5 years from manufacture to use. In another embodiment, within such packages, the elastomeric matrix is compressed within a retaining member to facilitate its loading into a delivery-device, such as a catheter or endoscope, in a compressed configuration. In another embodiment, the elastomeric matrix comprises an elastomer with a compression set enabling it to expand to a

substantial proportion of its pre-compressed volume, e.g., at 25°C, to at least 50% of its pre-compressed volume. In another embodiment, expansion occurs after the elastomeric matrix remains compressed in such a package for typical commercial storage and distribution times, which will commonly exceed 3 months and may be up to 1 or 5 years from manufacture to use. If desired, the reticulated elastomeric implants or implants can be rendered radiopaque to allow for visualization of the implants in situ by the clinician during and after the procedure, employing radioimaging. Any suitable radiopaque agent that can be covalently bound, adhered or otherwise attached to the reticulated polymeric implants may be employed including without limitation, tantalum, titanium and barium sulfate or other suitable material known to those skilled in the art. In addition to incorporating radiopaque agents such as tantalum into the implant material itself, a further embodiment of the invention encompasses the use of radiopaque metallic components to impart radiopacity to the implant. For example, thin filaments comprised of metals with or without shape memory properties such as platinum or nitinol can be embedded into the implant and may be in the form of a straight or curved wire, helical or coil-like structure, umbrella structure, or other structure generally known to those skilled in the art. Alternatively, a metallic frame around the implant may also be used to impart radiopacity. The metallic frame may be in the form of a tubular structure, a helical or coil-like structure, an umbrella structure, or other structure generally known to those skilled in the art. In one embodiment, the metallic implants incorporated in or surrounding the orthopedic or spinal implant for gripping or attachment or positioning or fastening of the implant at the target site can be used to impart radiopacity. Attachment of radiopaque metallic components to the implant can be accomplished by means including but not limited to chemical bonding or adhesion, suturing, pressure fitting, compression fitting, and other physical methods.

[00132] According to the invention the reticulated elastomeric matrix can be appropriately shaped to form a closure device to seal the access opening in the annulus resulting from a discotomy to reinforce and stabilize the disc annulus in case of

herniated disc, also known as disc prolapse or a slipped or bulging disc. The implantable device is compressed and delivered into the annulus opening by a trocar, cannula, or catheter with assisted visualization through an endoscopic intrument such as a laproscope, arthroscope, or cystoscope, preferably the cannula used during the discectomy procedure. In another embodiment, the implantable device is not compressed and delivered into the annulus opening by a trocar, cannula, or catheter with assisted visualization through an endoscopic intrument such as a laproscope, arthroscope, or cystoscope, preferably the cannula used during the discectomy procedure. The device can be secured into the opening by at least the following two mechanisms: first, the outwardly resilient nature of the reticulated solid phase can provide a mechanical means for preventing migration; and, second, the reticulated solid phase can serve as a scaffold to support fibrocartilage growth into the interconnected void phase of the elastomeric matrix. Additional securing may be obtained by the use of anchors, sutures or biological glues and adhesives, as known to those in the art. The closure device can support fibrocartilage ingrowth into the elastomeric matrix of the implantable device. Once released at the site, the reticulated elastomeric matrix expands resiliently to about its original, relaxed size and shape subject, of course, to its compression set limitation and any desired flexing, draping or other conformation to the site anatomy that the implantable device may adopt.

[00133] In one embodiment, cellular entities such as fibroblasts and tissues can invade and grow into the reticulated elastomeric matrix. In due course, such ingrowth can extend into the interior pores and interstices of the inserted reticulated elastomeric matrix. Eventually, the elastomeric matrix can become substantially filled with proliferating cellular ingrowth that provides a mass that can occupy the site or the void spaces in it. The types of tissue ingrowth possible include, but are not limited to, fibrous tissues and endothelial tissues.

[00134] In another embodiment, the implantable device or device system causes cellular ingrowth and proliferation throughout the site, throughout the site boundary,

or through some of the exposed surfaces, thereby sealing the site. Over time, this induced fibrovascular entity resulting from tissue ingrowth can cause the implantable device to be incorporated into the conduit. Tissue ingrowth can lead to very effective resistance to migration of the implantable device over time. It may also prevent recanalization of the conduit. In another embodiment, over the course of time, for example, for 2 weeks to 3 months to 1 year, the implanted reticulated elastomeric matrix becomes completely filled and/or encapsulated by tissue, fibrous tissue, scar tissue or the like.

[00135] The properties of the reticulated elastomeric matrix can be engineered to match the application by, e.g., controlling the amount of crosslinking, amount of crystallinity, chemical composition, chemical type of the solvent or solvent blend (when a solvent is used in processing), annealing conditions, curing conditions, and degree of reticulation. Unlike biodegradable polymers, when used as a scaffold, the reticulated elastomeric matrix maintains its physical characteristics and performance *in vivo* over long periods of time. Thus, it does not initiate undesirable tissue response as is observed for biodegradable implants when they break down and degrade. The high void content and degree of reticulation of the reticulated elastomeric matrix allows tissue ingrowth and proliferation of cells within the matrix. In one embodiment, the ingrown tissue and/or proliferated cells occupy from about 51% to about 99% of the volume of interconnected void phase of the original implantable device, thereby providing functionality, such as load bearing capability, of the original tissue that is being repaired or replaced.

EXAMPLES

[00136] Example 1- Fabrication of a Crosslinked Reticulated Polyurethane Matrix

[00137] Aromatic isocyanates, RUBINATE 9258 (from Huntsman; comprising a mixture of 4,4'-MDI and 2,4'-MDI), were used as the isocyanate component. RUBINATE 9258 contains about 68% by weight 4,4'-MDI, about 32% by weight 2,4'-MDI and has an isocyanate functionality of about 2.33 and is a liquid at at 25°C. A polyol - 1,6-hexamethylene carbonate (PC 1733, Stahl Chemicals) i.e., a diol, with a molecular weight of about 1,000 Daltons, was used as the polyol component and is a solid at 25°C. Glycerol was the chain extender,and water was used as the blowing agent. The blowing catalyst were tertiary amine 33% triethylenediamine in dipropylene glycol (DABCO 33LV supplied by Air Products) and Niax-A1 (supplied by Air Products). A silicone-based surfactant was used (TEGOSTAB® BF 2370, supplied by Goldschmidt). The cell-opener was ORTEGOL® 501 (supplied by Goldschmidt). A viscosity depressant (Propylene carbonate supplied by Sigma-Aldrich) was also used. The proportions of the components that were used is given in the following table:

Table 1

Ingredient	Parts by Weight
Polyol Component -PC 1733, Stahl Chemicals Glycerine	100
Viscosity Depressant - Propylene carbonate	4.92
Surfactant - TEGOSTAB® BF 2370	11.6
Cell Opener - ORTEGOL® 501	4.40
Isocyanate Component RUBINATE 9258	4.0
Isocyanate Index	99.78
Distilled Water	1.00
Blowing Catalyst Dabco 33 LV	3.36
Blowing Catalyst Niax-A1	1.0
	0.06

[00138] The polyol was liquefied at 70 °C in an air circulation oven, and was weighed into a polyethylene cup. Viscosity depressant (propylene carbonate) was added to the polyol and mixed with a drill mixer equipped with a mixing shaft at 3100 rpm for 15 seconds (mix-1). Surfactant (Tegostab BF-2370) was added to mix-1 and mixed for additional 15 seconds (mix-2). Cell opener (Ortogel 501) was added to mix-2 and mixed for 15 seconds (mix-3). Isocyanate (Rubinate 9258) was added to mix-3 and mixed for 60±10 seconds (system A).

[00139] Distilled water was mixed with both blowing catalyst (Dabco 33LV and Niax A1) and glycerine in a small plastic cup by using a tiny glass rod for 60 seconds (System B).

[00140] System B was poured into System A as quickly as possible without spilling and with vigorous mixing with a drill mixer for 10 seconds and poured into cardboard box of 9 in. x 8 in. x 5 in., which is covered inside with aluminum foil. The foaming profile was as follows: mixing time of 10 sec., cream time of 18 sec. and rise time of 75 sec.

[00141] Two minutes after beginning of foam mixing, the foam was placed in the oven at 100 – 105°C for curing for 65 minutes. The foam is taken from the oven and cooled for 15 minutes at room temperature. The skin was cut with the band saw, and the foam was pressed by hand from all sides to open the cell windows. The foam was put back into an air-circulation oven for post-curing at 100° – 105°C for an additional 5 hours.

[00142] The average pore diameter of the foam, as observed by optical microscopy, as shown in the micrographs of Figures 15 and 16, was between 150 and 300 μm.

[00143] The subsequent foam testing was carried out in accordance with ASTM D3574. Density was measured with specimens measuring 50 mm x 50 mm x 25 mm. The density was calculated by dividing the weight of the sample by the volume of the specimen; a value of 2.75 lbs/ft^3 was obtained.

[00144] Tensile tests were conducted on samples that were cut both parallel and perpendicular to the direction of foam rise. The dog-bone shaped tensile specimens were cut from blocks of foam each about 12.5 mm thick, about 25.4 mm wide and about 140 mm long. Tensile properties (strength and elongation at break) were measured using an INSTRON Universal Testing Instrument Model 1122 with a cross-head speed of 500 mm/min (19.6 inches/minute). The average tensile strength, measured from two orthogonal directions parallel and perpendicular with respect to foam rise, were 67.6 psi and 56.44 psi, respectively. The elongation to break was approximately 46 %.

[00145] In the subsequent reticulation procedure, a block of foam was placed into a pressure chamber, the doors of the chamber were closed and an airtight seal was maintained. The pressure was reduced to remove substantially all of the air in the foam. A combustible ratio of hydrogen to oxygen gas was charged into the chamber for enough time to permeate all the samples. The gas in the chamber was then ignited by a spark plug. The ignition exploded the gasses within the foam cell structure. This explosion blew out many of the foam cell windows, thereby creating a reticulated elastomeric matrix structure.

[00146] Example 2 - Fabrication of a Crosslinked Reticulated Polyurethane Matrix

[00147] Aromatic isocyanates, RUBINATE 9258 (from Huntsman; comprising a mixture of 4,4'-MDI and 2,4'-MDI), were used as the isocyanate component. RUBINATE 9258 contains about 68% by weight 4,4'-MDI, about 32% by weight 2,4'-MDI and has an isocyanate functionality of about 2.33 and is a liquid at at 25°C. A polyol - 1,6-hexamethylene carbonate (Desmophen LS 2391, Bayer Polymers), i.e., a diol, with a molecular weight of about 2,000 Daltons, was used as the polyol component and is a solid at 25°C. Water was used as the blowing agent. The blowing catalyst was the tertiary amine 33% triethylenediamine in dipropylene glycol (DABCO 33LV supplied by Air Products). A silicone-based surfactant was used

(TEGOSTAB® BF 2370, supplied by Goldschmidt). The cell-opener was ORTEGOL® 501 (supplied by Goldschmidt). A viscosity depressant (Propylene carbonate supplied by Sigma-Aldrich) was also used. The proportions of the components that were used is given the following table:

Table 2

Ingredient	Parts by Weight
Polyol Component - Desmophen LS 2391	100
Viscosity Depressant - Propylene carbonate	5.76
Surfactant - TEGOSTAB® BF 2370	2.16
Cell Opener - ORTEGOL® 501	0.48
Isocyanate Component RUBINATE 9258	53.8
Isocyanate Index	1.00
Distilled Water	2.82
Blowing Catalyst	0.44

[00148] The polyol Desmophen LS 2391 was liquefied at 70 °C in an air circulation oven, and 150 gms of it was weighed into a polyethylene cup. 8.7 g of viscosity depressant (propylene carbonate) was added to the polyol and mixed with a drill mixer equipped with a mixing shaft at 3100 rpm for 15 seconds (mix-1). 3.3 g of surfactant (Tegostab BF-2370) was added to mix-1 and mixed for additional 15 seconds (mix-2). 0.75 g of cell opener (Ortogel 501) was added to mix-2 and mixed for 15 seconds (mix-3). 80.9 g of isocyanate (Rubinate 9258) is added to mix-3 and mixed for 60±10 seconds (System A).

[00149] 4.2 g of distilled water was mixed with 0.66 g of blowing catalyst (Dabco 33LV) in a small plastic cup by using a tiny glass rod for 60 seconds (System B).

[00150] System B was poured into System A as quickly as possible without spilling and with vigorous mixing with a drill mixer for 10 seconds and poured into cardboard box of 9 in. x 8 in. x 5 in., which was covered inside with aluminum foil. The foaming profile was as follows: mixing time of 10 sec., cream time of 18 sec. and rise time of 85 sec.

[00151] Two minutes after beginning of foam mixing, the foam was placed in the oven at 100 – 105°C for curing for 60minutes. The foam is taken from the oven and cooled for 15 minutes at room temperature. The skin is cut with the band saw, and the foamwais pressed by hand from all sides to open the cell windows. The foam was put back in an air-circulation oven for postcuring at 100° – 105°C for additional 5 hours.

[00152] The average pore diameter of the foam, as observed by optical microscopy, as shown in Figures 17 and 18, was between 150 and 450 μm.

[00153] Subsequent foam testing was carried out in accordance with ASTM D3574. Density was measured with specimens measuring 50 mm x 50 mm x 25 mm. The density was calculated by dividing the weight of the sample by the volume of the

specimen; a value of 2.5 lbs/ft^3 was obtained.

[00154] Tensile tests were conducted on samples that were cut both parallel and perpendicular to the direction of foam rise. The dog-bone shaped tensile specimens were cut from blocks of foam each about 12.5 mm thick, about 25.4 mm wide and about 140 mm long. Tensile properties (strength and elongation at break) were measured using an INSTRON Universal Testing Instrument Model 1122 with a cross-head speed of 500 mm/min (19.6 inches/minute). The average tensile strength, measured from two orthogonal directions with respect to foam rise, was 24.64 $\pm$ 2.35 psi. The elongation to break was approximately 215 $\pm$ 12 %.

[00155] Compressive strengths of the foam were measured with specimens measuring 50 mm x 50 mm x 25 mm. The tests were conducted using an INSTRON Universal Testing Instrument Model 1122 with a cross-head speed of 10 mm/min (0.4 inches /min). The compressive strength at 50% was about 12 $\pm$ 3 psi. The compression set after subjecting the sample to 50 % compression for 22 hours at 40 °C and releasing the stress was 2 %.

[00156] Tear resistance strength of the foam was measured with specimens measuring approximately 152 mm x 25 mm x 12.7 mm. A 40 mm cut was made on one side of each specimen. The tear strength was measured using an INSTRON Universal Testing Instrument Model 1122 with a cross-head speed of 500 mm/min (19.6 inches/minute). The tear strength was determined to be about 2.9 $\pm$ 0.1lbs/inch.

[00157] The pore structure and its inter-connectivity is measured by Liquid Extrusion Porosimeter (manufactured by Porous Materials, Inc. (Ithaca, NY). In this test, the pores of a 25.4 mm diameter sample is filled with a wetting fluid having a surface tension of 19 dynes/cm and loaded in a sample chamber with a 27 micron diameter pore membrane being placed under the sample . The pressure of air in the chamber space above the wetted sample is increased slowly so that the liquid is extruded from the pores of the sample. For low surface tension fluid, the contact

angle is taken to be zero and the wetting liquid that spontaneously fills the pore of the test sample also spontaneously fill the pores of the membranes when the former is emptied under pressure with larger pores emptying out at lower pressures and smaller pores emptying out at higher pressure. The displaced liquid passes through the membrane and its volume measured. The differential pressure p required to displace liquid from a pore is related to its diameter D, surface tension of the liquid γ and the contact angle θ by the relation $p= 4 \gamma \cos \theta/D$. The gas pressure gives the pore diameter and the volume of the displaced liquid gives the pore volume or the intrusion volume accessible to the low surface tension liquid. Again measurement of liquid flow (water in this case) without the membrane under the sample and using similar pressure-flow methods yields liquid permeability. The liquid intrusion volume for the foam is 4 cc/gm and permeability of water through the foam is 1 lit/min/psi/sq cm.

[00158] In the subsequent reticulation procedure, a block of foam was placed into a pressure chamber, the doors of the chamber are closed, and an airtight seal was maintained. The pressure is reduced to remove substantially all of the air in the foam. A combustible ratio of hydrogen to oxygen gas was charged into the chamber for enough time to permeate all the samples. The gas in the chamber was then ignited by a spark plug. The ignition explodes the gasses within the foam cell structure. This explosion blew out many of the foam cell windows, thereby creating a reticulated elastomeric matrix structure.

[00159] Tensile tests were conducted on reticulated samples that were cut both parallel and perpendicular to the direction of foam rise. The dog-bone shaped tensile specimens were cut from blocks of foam each about 12.5 mm thick, about 25.4 mm wide and about 140 mm long. Tensile properties (strength and elongation at break) were measured using an INSTRON Universal Testing Instrument Model 1122 with a cross-head speed of 500 mm/min (19.6 inches/minute). The average tensile strength, measured from two orthogonal directions with respect to foam rise, was 23.5 psi. The elongation to break was approximately 194 %.

[00160] Post reticulation compressive strengths of the foam were measured with specimens measuring 50 mm x 50 mm x 25 mm. The tests were conducted using an INSTRON Universal Testing Instrument Model 1122 with a cross-head speed of 10 mm/min (0.4 inches /min). The compressive strength at 50% was about 6.5 psi.

[00161] The pore structure and its inter-connectivity is measured by Liquid Extrusion Porosimeter. The liquid intrusion volume for the reticulated foam is 28 cc/gm and permeability of water through the foam is 413 lit/min/psi/sq cm. The results demonstrate the interconnected and continuous pore structure of the reticulated foam compared to the un-reticulated foam.

[00162] Example 3 -Fabrication of a Crosslinked Polyurethane Matrix

[00163] The aromatic isocyanate RUBINATE 9258 (from Huntsman) was used as the isocyanate component. RUBINATE 9258, which is a liquid at 25°C, contains 4,4'-MDI and 2,4'-MDI and has an isocyanate functionality of about 2.33. A diol, poly(1,6-hexanecarbonate)diol (POLY-CD CD220 from Arch Chemicals) with a molecular weight of about 2,000 Daltons was used as the polyol component and was a solid at 25°C. Distilled water was used as the blowing agent. The blowing catalyst used was the tertiary amine triethylenediamine (33% in dipropylene glycol; DABCO 33LV from Air Products). A silicone-based surfactant was used (TEGOSTAB® BF 2370 from Goldschmidt). A cell-opener was used (ORTEGOL® 501 from Goldschmidt). The viscosity modifier propylene carbonate (from Sigma-Aldrich) was present to reduce the viscosity. The proportions of the components that were used are set forth in the following table:

Table 3

Ingredient	Parts by Weight
Polyol Component	100
Viscosity Modifier	5.80
Surfactant	0.66
Cell Opener	1.00
Isocyanate Component	47.25
Isocyanate Index	1.00
Distilled Water	2.38
Blowing Catalyst	0.53

[00164] The polyol component was liquefied at 70°C in a circulating-air oven, and 100 g thereof was weighed out into a polyethylene cup. 5.8 g of viscosity modifier was added to the polyol component to reduce the viscosity, and the ingredients were mixed at 3100 rpm for 15 seconds with the mixing shaft of a drill mixer to form "Mix-1". 0.66 g of surfactant was added to Mix-1, and the ingredients were mixed as described above for 15 seconds to form "Mix-2". Thereafter, 1.00 g of cell opener was added to Mix-2, and the ingredients were mixed as described above for 15 seconds to form "Mix-3". 47.25 g of isocyanate component were added to Mix-3, and the ingredients were mixed for 60 ± 10 seconds to form "System A".

[00165] 2.38 g of distilled water was mixed with 0.53 g of blowing catalyst in a small plastic cup for 60 seconds with a glass rod to form "System B".

[00166] System B was poured into System A as quickly as possible while avoiding spillage. The ingredients were mixed vigorously with the drill mixer as described above for 10 seconds and then poured into a 22.9 cm x 20.3 cm x 12.7 cm (9 in. x 8 in. x 5 in.) cardboard box with its inside surfaces covered by aluminum foil. The foaming profile was as follows: 10 seconds mixing time, 17 seconds cream time, and 85 seconds rise time.

[00167] Two minutes after the beginning of foaming, i.e., the time when Systems A and B were combined, the foam was placed into a circulating-air oven maintained at 100-105°C for curing for from about 55 to about 60 minutes. Then, the foam was removed from the oven and cooled for 15 minutes at about 25°C. The skin was removed from each side using a band saw. Thereafter, hand pressure was applied to each side of the foam to open the cell windows. The foam was replaced into the circulating-air oven and postcured at 100-105°C for an additional four hours.

[00168] The average pore diameter of the foam, as determined from optical microscopy observations, was greater than about 275 μm.

[00169] The following foam testing was carried out according to ASTM D3574: Bulk density was measured using specimens of dimensions 50 mm x 50 mm x 25 mm. The density was calculated by dividing the weight of the sample by the volume of the specimen. A density value of 2.81 lbs/ft^3 (0.0450 g/cc) was obtained.

[00170] Tensile tests were conducted on samples that were cut either parallel to or perpendicular to the direction of foam rise. The dog-bone shaped tensile specimens were cut from blocks of foam. Each test specimen measured about 12.5 mm thick, about 25.4 mm wide, and about 140 mm long; the gage length of each specimen was 35 mm and the gage width of each specimen was 6.5 mm. Tensile properties (tensile strength and elongation at break) were measured using an INSTRON Universal Testing Instrument Model 1122 with a cross-head speed of 500 mm/min (19.6 inches/minute). The average tensile strength perpendicular to the direction of foam rise was determined as 29.3 psi (20,630 kg/m^2). The elongation to break perpendicular to the direction of foam rise was determined to be 266%.

[00171] The measurement of the liquid flow through the material is measured in the following way using a iquid permeability apparatus or Liquid Permeaeter (Porous Materials, Inc., Ithaca, NY). The foam sample was 8.5 mm in thickness and covered a hole 6.6 mm in diameter in the center of a metal plate that was placed at the bottom of

the Liquid Permeaeter filled with water. Thereafter, the air pressure above the sample was increased slowly to extrude the liquid from the sample and the permeability of water through the foam was determined to be 0.11 L/min/psi/cm^2.

[00172] Example 4 - Reticulation of a Crosslinked Polyurethane Foam

[00173] Reticulation of the foam described in Example 3 was carried out by the following procedure: A block of foam measuring approximately 15.25 cm x 15.25 cm x 7.6 cm (6 in. x 6 in. x 3 in.) was placed into a pressure chamber, the doors of the chamber were closed, and an airtight seal to the surrounding atmosphere was maintained. The pressure within the chamber was reduced to below about 100 millitorr by evacuation for at least about two minutes to remove substantially all of the air in the foam. A mixture of hydrogen and oxygen gas, present at a ratio sufficient to support combustion, was charged into the chamber over a period of at least about three minutes. The gas in the chamber was then ignited by a spark plug. The ignition exploded the gas mixture within the foam. The explosion was believed to have at least partially removed many of the cell walls between adjoining pores, thereby forming a reticulated elastomeric matrix structure.

[00174] The average pore diameter of the reticulated elastomeric matrix, as determined from optical microscopy observations, was greater than about 275 μm. A scanning electron micrograph image of the reticulated elastomeric matrix of this example (not shown here) demonstrated, e.g., the communication and interconnectivity of pores therein.

[00175] The density of the reticulated foam was determined as described above in Example 3. A post-reticulation density value of 2.83 lbs/ft^3 (0.0453 g/cc) was obtained.

[00176] Tensile tests were conducted on reticulated foam samples as described above in Example 3. The average post-reticulation tensile strength perpendicular to the direction of foam rise was determined as about 26.4 psi (18,560 kg/m^2). The post-

reticulation elongation to break perpendicular to the direction of foam rise was determined to be about 250%. The average post-reticulation tensile strength parallel to the direction of foam rise was determined as about 43.3 psi (30,470 kg/m^2). The post-reticulation elongation to break parallel to the direction of foam rise was determined to be about 270%.

[00177] Compressive tests were conducted using specimens measuring 50 mm x 50 mm x 25 mm. The tests were conducted using an INSTRON Universal Testing Instrument Model 1122 with a cross-head speed of 10 mm/min (0.4 inches /minute). The post-reticulation compressive strengths at 50% compression, parallel to and perpendicular to the direction of foam rise, were determined to be 1.53 psi (1,080 kg/m^2) and 0.95 psi (669 kg/m^2), respectively. The post-reticulation compressive strengths at 75% compression, parallel to and perpendicular to the direction of foam rise, were determined to be 3.53 psi (2,485 kg/m^2) and 2.02 psi (1,420 kg/m^2), respectively. The post-reticulation compression set, determined after subjecting the reticulated sample to 50% compression for 22 hours at 25°C then releasing the compressive stress, parallel to the direction of foam rise, was determined to be about 4.5%.

[00178] The resilient recovery of the reticulated foam was measured by subjecting 1 inch (25.4 mm) diameter and 0.75 inch (19 mm) long foam cylinders to 75% uniaxial compression in their length direction for 10 or 30 minutes and measuring the time required for recovery to 90% ("t-90%") and 95% ("t-95%") of their initial length. The percentage recovery of the initial length after 10 minutes ("r-10") was also determined. Separate samples were cut and tested with their length direction parallel to and perpendicular to the foam rise direction. The results obtained from an average of two tests are shown in the following table:

Table 4

Time compressed (min)	Test Sample Orientation	t-90% (sec)	t-95% (sec)	r-10 (%)
10	Parallel	6	11	100
10	Perpendicular	6	23	100
30	Parallel	9	36	99
30	Perpendicular	11	52	99

[00179] In contrast, a comparable foam with little to no reticulation typically has t-90 values of greater than about 60-90 seconds after 10 minutes of compression.

[00180] The measurement of the liquid flow through the material was measured in the following way using a Liquid permeability apparatus or Liquid Permeaeter (Porous Materials, Inc., Ithaca, NY). The foam samples were between 7.0 and 7.7 mm in thickness and covered a hole 8.2 mm in diameter in the center of a metal plate that was placed at the bottom of the Liquid Permeaeter filled with water. The water was allowed to extrude through the sample under gravity and the permeability of water through the foam was determined to be 180 L/min/psi/cm^2 in the direction of foam rise and 160 L/min/psi/cm^2 in the perpendicular to foam rise.

[00181] Example 5 - Fabrication of a Crosslinked Reticulated Polyurethane Matrix

[00182] A crosslinked Polyurethane Matrix was made using similar starting materials and following procedures similar to the one described in Example 3. Glycerol was used as an additional starting material. The proportions of the components that were used are set forth in the following table:

Table 5

Ingredient	Parts by Weight
PolyCD™CD220(g)	100
Propylene carbonate (g)	5.80
Tegostab BF-2370 (g)	1.50
Ortegol 501 (g)	1.00
Rubinate 9258 (g)	49.29
Distiled water) (g)	1.80
Dabco 33 LV (g)	0.50
Glycerine (g)	2.46

[00183] The reaction profile is as follows:

Mixing time	10
Cream time	27
Rise time	120

[00184] The average pore diameter of the foam, as determined from optical microscopy observations, was greater than about 225 μm.

[00185] The following foam testing was carried out according to ASTM D3574: Bulk density was measured using specimens of dimensions 50 mm x 50 mm x 25 mm. The density was calculated by dividing the weight of the sample by the volume of the specimen. A density value of 3.65 lbs/ft^3 (0.060 g/cc) was obtained.

[00186] Tensile tests were conducted on samples that were cut perpendicular to the direction of foam rise. The dog-bone shaped tensile specimens were cut from blocks of foam. Each test specimen measured about 12.5 mm thick, about 25.4 mm wide, and about 140 mm long; the gage length of each specimen was 35 mm and the gage width of each specimen was 6.5 mm. Tensile properties (tensile strength and elongation at break) were measured using an INSTRON Universal Testing Instrument Model 1122 with a cross-head speed of 500 mm/min (19.6 inches/minute). The

average tensile strength perpendicular to the direction of foam rise was determined as 37.8 psi (26,500 kg/m^2). The elongation to break perpendicular to the direction of foam rise was determined to be 141%.

[00187] Reticulation of the foam described above was carried out by the following procedure: A block of foam measuring approximately 15.25 cm x 15.25 cm x 7.6 cm (6 in. x 6 in. x 3 in.) was placed into a pressure chamber, the doors of the chamber were closed, and an airtight seal to the surrounding atmosphere was maintained. The pressure within the chamber was reduced to below about 100 millitorr by evacuation for at least about two minutes to remove substantially all of the air in the foam. A mixture of hydrogen and oxygen gas, present at a ratio sufficient to support combustion, was charged into the chamber over a period of at least about three minutes. The gas in the chamber was then ignited by a spark plug. The ignition exploded the gas mixture within the foam. The explosion was believed to have at least partially removed many of the cell walls between adjoining pores, thereby forming a reticulated elastomeric matrix structure.

[00188] A scanning electron micrograph image of the reticulated elastomeric matrix of this example (not shown here) demonstrated, e.g., the communication and interconnectivity of pores therein.

[00189] The density of the reticulated foam was determined as described above and a value of 4.00 lbs/ft^3 (0.0656 g/cc) was obtained.

[00190] Tensile tests were conducted on reticulated foam samples as described above and the average post-reticulation tensile strength perpendicular to the direction of foam rise was determined as about 35.3 psi (24,680 kg/m^2). The post-reticulation elongation to break perpendicular to the direction of foam rise was determined to be about 125%.

[00191] Compressive tests were conducted using specimens measuring 50 mm x 50 mm x 25 mm. The tests were conducted using an INSTRON Universal Testing

Instrument Model 1122 with a cross-head speed of 10 mm/min (0.4 inches /minute). The post-reticulation compressive strengths perpendicular to the direction of foam rise at 50% and 75 % compression strains were determined to be 3.83 psi (2,680 kg/m^2) and 9.33 psi (6,530 kg/m^2), respectively.

[00192] Example 6 – Testing in a Rabbit Model

[00193] An example of a device according to the invention, a cylindrical scaffold of reticulated polycarbonate prepared consistent with Examples 3 to 5, referred to as the "ARDX implant", was used for annular repair in the rabbit model of degenerative disc disease. This model is considered a standard model to evaluate the vertebral disc. See, for example, H.S. An et al., "Biological Repair of Intervertebral Disc," Spine, 2003 Aug. 1; 28 (15 Suppl.); D.G. Anderson et al., "Comparative Gene Expression Profiling of Normal and degenerative Discs: Analysis of a Rabbit Annular Laceration Mode," Spine. 2002 Jun 15; 27(12): 1291-96; and M.W. Kroeber et al., "New *in Vivo* Animal Model to Create Intervertebral Disc Degeneration and to Investigate the Effects of Therapeutic Strategy to Stimulate Disc Regeneration," Spine, 2002 Dec. 1; 27(23): 2684-90. Four adult female New Zealand rabbits were utilized for the experiment. Under a general anesthetic via a posterior-lateral approach, the lumbar spine was exposed. The annulus of disc spaces from L1 to L5 were then incised in with a #15 scalpel laterally to induce the traumatic injury. Three of the annular defects were repaired with the ARDX implant, which was positioned into the spinal annular defect and secured with a non-resorbable suture. The fourth disc space was left un-repaired as a control. The animals were sacrificed at four weeks, and the spinal segments were processed for histology with H&E and SO stains. The findings at harvest showed excellent tolerance of the implants and grossly maintained disc space. The histology showed the preservation of the disc space and intact nucleus.

[00194] The ARDX implant was well integrated with good tissue in-growth, as is shown in the micrograph (No2L45 SO stain 100x) of Fig. 19 and the closeup view in Fig. 20, where the implant 130 abuts nucleus 132 adjacent to annulus 134. Annulus

134 is in turn adjacent to vertebral end plate 136. In the detail shown in Fig. 20 new tissue growth 138 can be seen. A strut or projection 140 from implant 130 can be seen. The early regeneration of matrix secretion and organized collagen fibers preserved the disc space and prevented degeneration when compared to control samples.

[00195] Overall the ARDX implant device promoted repair and regeneration of spinal annulus and disc in the rabbit model.

[00196] While illustrative embodiments of the invention have been described above, it is, of course, understood that many and various modifications will be apparent to those in the relevant art, or may become apparent as the art develops. Such modifications are contemplated as being within the spirit and scope of the invention or inventions disclosed in this specification.

We Claim:

1. An apparatus that comprises a scaffold comprised of a biodurable, resiliently compressible, elastomeric reticulated composition to repair and/or regenerate spinal/vertebral connective tissue defects.

2. An apparatus that comprises a scaffold comprised of a biodurable, resiliently compressible, elastomeric reticulated composition to repair and/or regenerate spinal-annular nuclear tissue defects.

3. An apparatus that comprises a tissue scaffold comprised of a biodurable, resiliently compressible, elastomeric reticulated composition for spinal annulo-nucleoplasty regeneration.

4. An apparatus for one of Claims 1 to 3 that comprises an at least partially cylindrical member.

5. The apparatus of Claim 4, wherein, when the elastomeric composition is compressed from a relaxed configuration to a first, compact configuration for delivery via a delivery-device, it expands to a second, working configuration, *in vitro*, at least about 80% of the size of the relaxed configuration in at least one dimension.

6. The apparatus of Claim 5, wherein the recovery properties of the elastomeric composition are such that a dimension of the second, working configuration is within about 20% of a relaxed dimension of the relaxed configuration after compression to from about 50 to about 10% of the relaxed dimension.5.

7. The apparatus of Claim 4, wherein the elastomeric composition is hydrophobic.

8. The apparatus of Claim 4, wherein the elastomeric composition comprises a thermoplastic elastomer selected from the group consisting of

polycarbonate polyurethanes, polyester polyurethanes, polyether polyurethanes, polysiloxane polyurethanes, polyurethanes with mixed soft segments, polycarbonates, polyesters, polyethers, polysiloxanes, polyurethanes, and mixtures of two or more thereof.

9. The apparatus of Claim 8, wherein the elastomeric composition comprises polyurethane.

10. The apparatus of Claim 8, wherein the elastomeric composition comprises a polycarbonate polyurethane.

11. The apparatus of Claim 8, wherein the thermoplastic elastomer is prepared by reacting a polyol component with an isocynanate component.

12. The apparatus of Claim 11, wherein the polyol component comprises a polycarbonate polyol, hydrocarbon polyol, polysiloxane polyol, poly(carbonate-co-hydrocarbon) polyol, poly(carbonate-co-siloxane) polyol, poly(hydrocarbon-co-siloxane) polyol, or mixtures thereof.

13. The apparatus of Claim 11, wherein the polyol component comprises a difunctional polycarbonate diol.

14. The apparatus of Claim 11, wherein the isocyanate component comprises tetramethylene diisocyanate, cyclohexane-1,2-diisocyanate, cyclohexane-1,4-diisocyanate, hexamethylene diisocyanate, isophorone diisocyanate, methylene-bis-(p-cyclohexyl isocyanate), p-phenylene diisocyanate, 4,4'-diphenylmethane diisocyanate, 2,4'-diphenylmethane diisocyanate, 2,4-toluene diisocyanate, 2,6-toluene diisocyanate, m-tetramethylxylene diisocyanate, or mixtures thereof.

15. The apparatus of Claim 11, wherein the isocyanate component comprises MDI, wherein the MDI is a mixture of at least about 5% by weight of 2,4'-MDI with the balance 4,4'-MDI.

16. The apparatus of Claim 4, wherein the elastomeric composition comprises a reticulated elastomeric matrix comprising a plurality of pores, the pores having an average diameter or other largest transverse dimension of at least about 20 μm.

17. The apparatus of Claim 16, wherein the pores have an average diameter or other largest transverse dimension of from about 20 μm to about 150 μm.

18. The apparatus of Claim 16, wherein the pores have an average diameter or other largest transverse dimension of from about 150 μm to about 250 μm.

19. The apparatus of Claim 16, wherein the pores have an average diameter or other largest transverse dimension of from about 250 μm to about 500 μm.

20. The apparatus of Claim 4, wherein the elastomeric matrix has a compressive strength at 50% compression of from about 1 to about 500 psi, a tensile strength of from about 1 to about 500 psi, and an ultimate tensile elongation of at least about 25%.

21. The apparatus of Claim 4, wherein the elastomeric composition has a compression set after 22 hours compression at about 25°C to 25% of its thickness in one dimension of not more than about 50%.

22. The apparatus of Claim 4, wherein the reticulated elastomeric matrix is configured to permit cellular ingrowth and proliferation into the elastomeric matrix.

23. The apparatus of Claim 4, endoporously coating a reticulated elastomeric matrix with a coating material selected to encourage cellular ingrowth and proliferation.

24. The apparatus of Claim 4, wherein the coating material comprises a foamed coating of a biodegradable material, the biodegradable material comprising collagen, fibronectin, elastin, hyaluronic acid or mixtures thereof.

25. The apparatus of Claim 4, wherein the implantable device comprises a plurality of elastomeric matrices.

26. The apparatus of Claim 4 which comprises a structural component adapted to maintain the scaffold in a desired location.

27. The apparatus of Claim 26, wherein the structural component comprises a compressible element at least partially within the scaffold that compresses during delivery and expands or releases upon delivery to engage tissue.

28. The apparatus of Claim 27, wherein the structural component comprises a longitudinal shaft member with umbrella-like spokes.

29. The apparatus of Claim 27, wherein the structural component comprises one or more arrangements of radial projections.

30. The apparatus of Claim 29 which can be rotated in one direction to engage tissue and in another direction to disengage tissue.

31. A system for treating a spinal annular defect which comprises an apparatus of Claim 4 and a delivery means.

32. The system of Claim 31, wherein the delivery means is a cannula, trocar, catheter, laproscope, or endoscope.

33. A method of treating spinal annular defects which comprises:

(a) inserting an apparatus of Claim 4 into the lumen of a delivery means;

(b) advancing the distal tip of the delivery means into an

opening in an annulus;

(c) advancing the apparatus through the lumen into the opening; and

(d) withdrawing the delivery means, whereby the apparatus expands into the opening.

34. The method of Claim 33, wherein the delivery vehicle is a trocar, cannula, or catheter, with visual assistance through an endoscopic instrument.

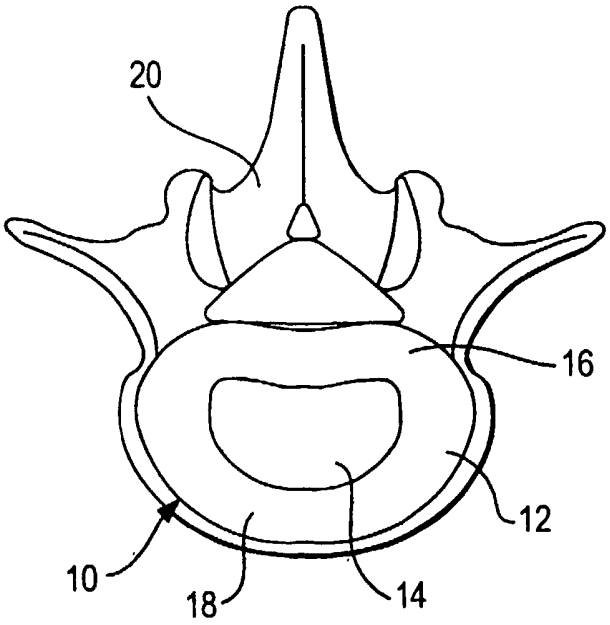

FIG. 1

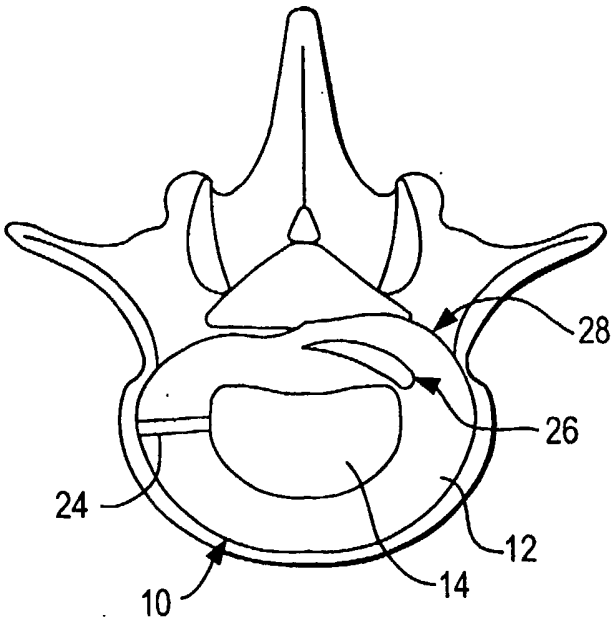

FIG. 2

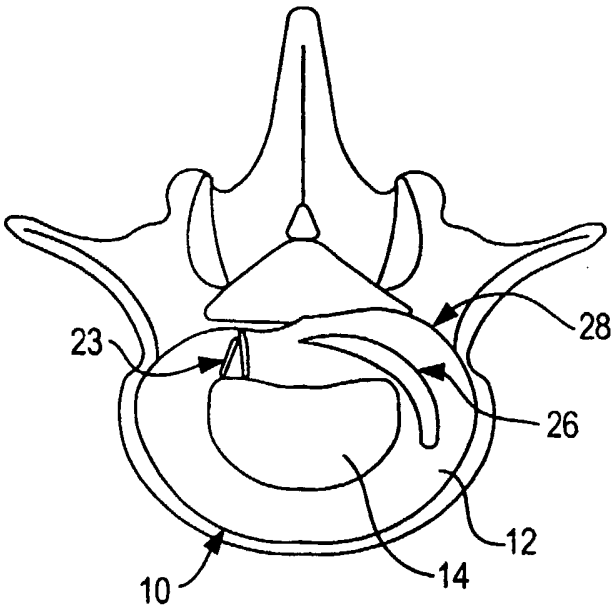

FIG. 3

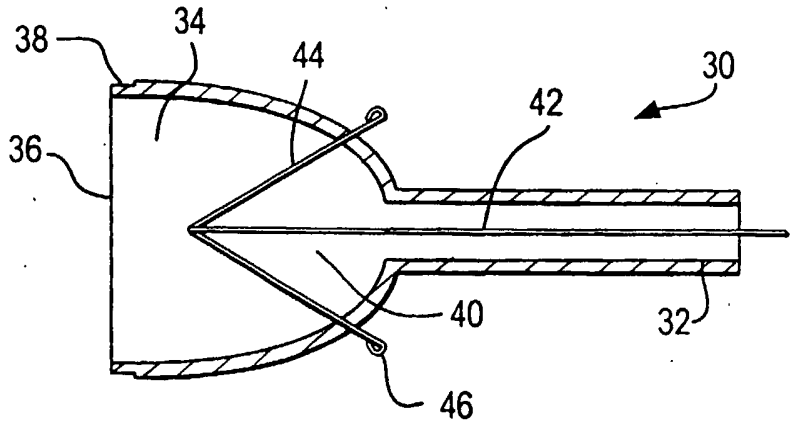

FIG. 4

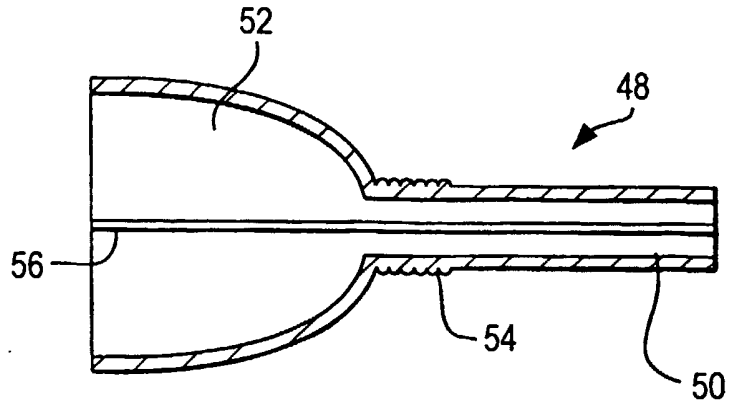

FIG. 5

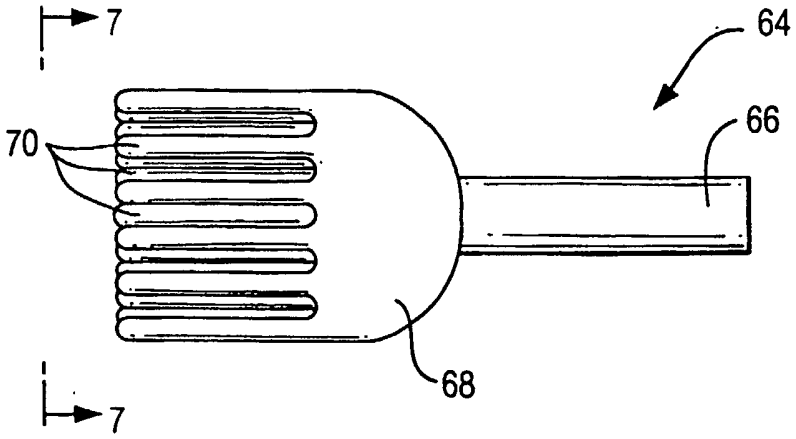

FIG. 6

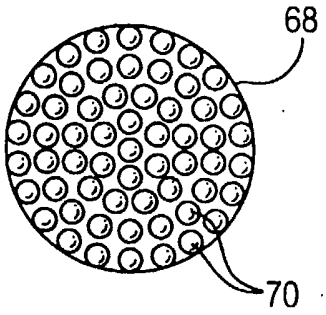

FIG. 7

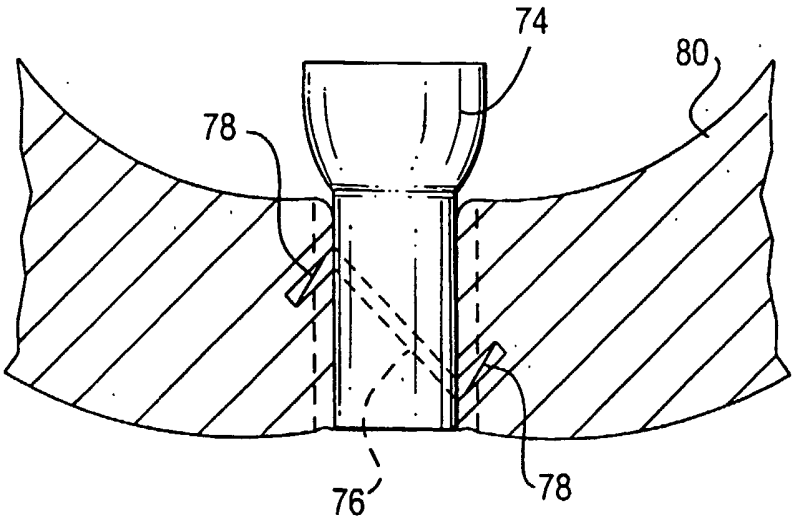

FIG. 8

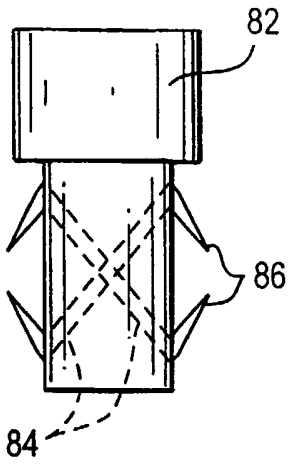

FIG. 9

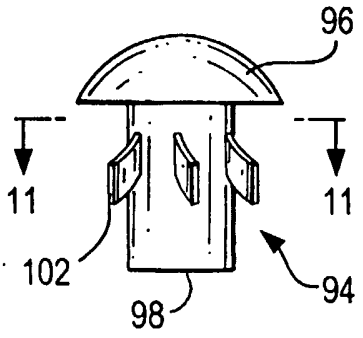

FIG. 10

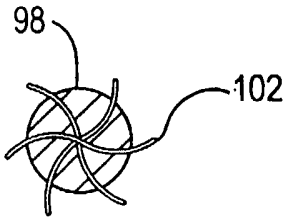

FIG. 11

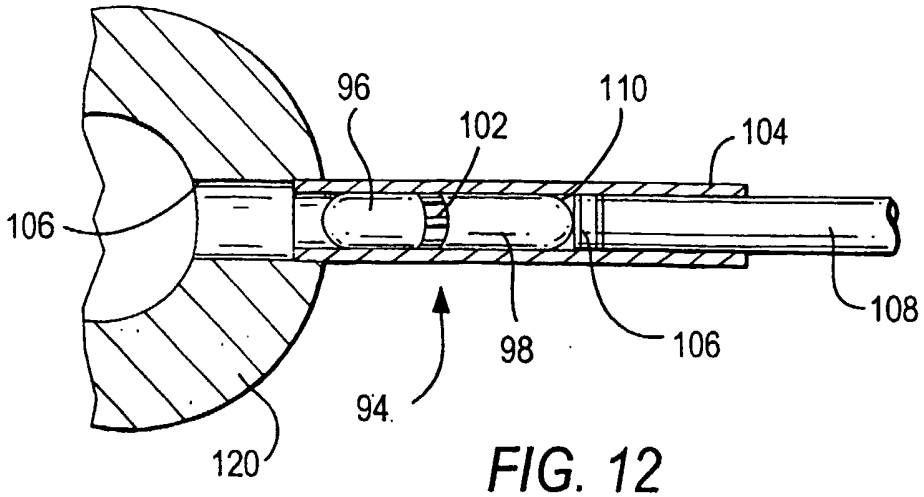

FIG. 12

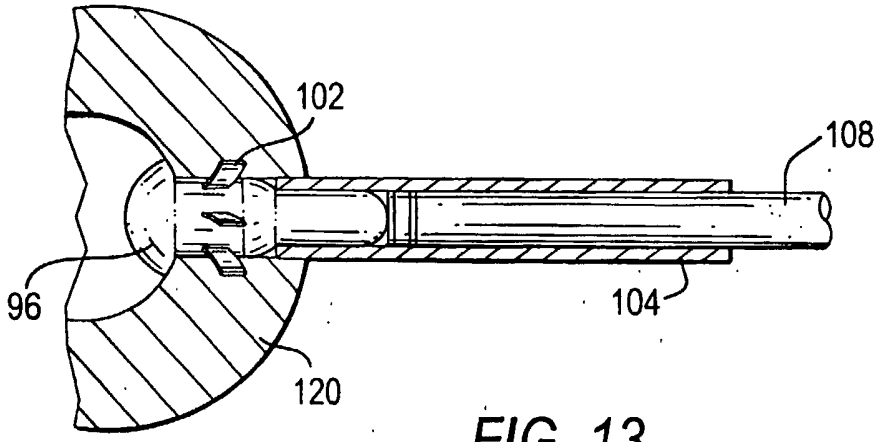

FIG. 13

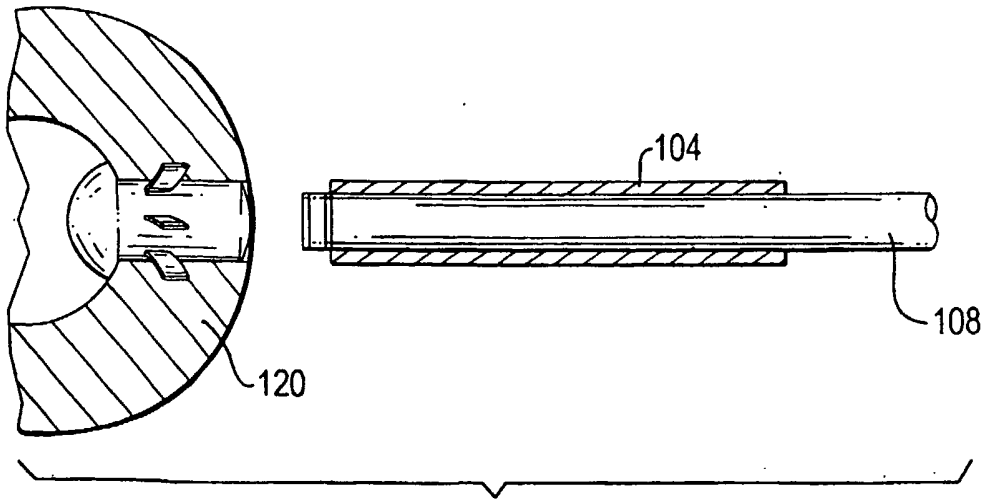

FIG. 14

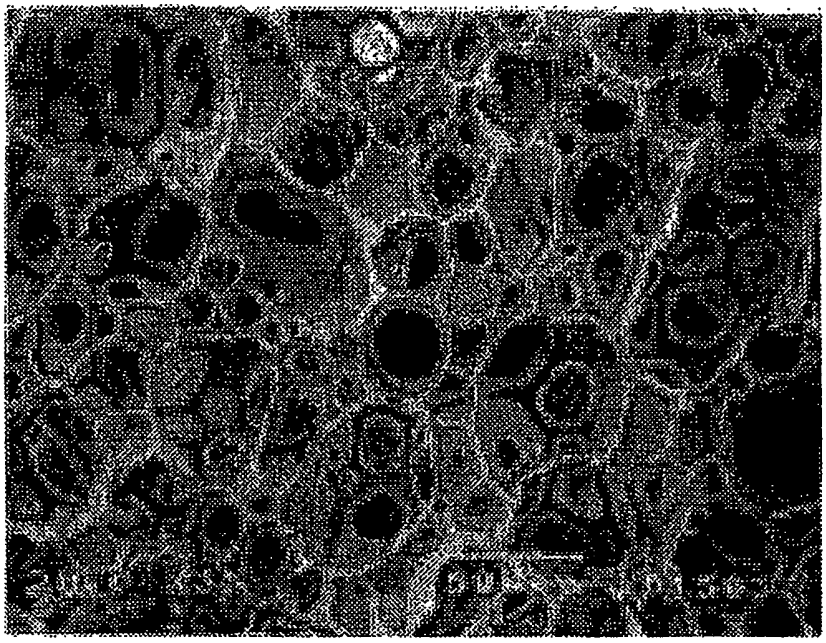

FIG. 15

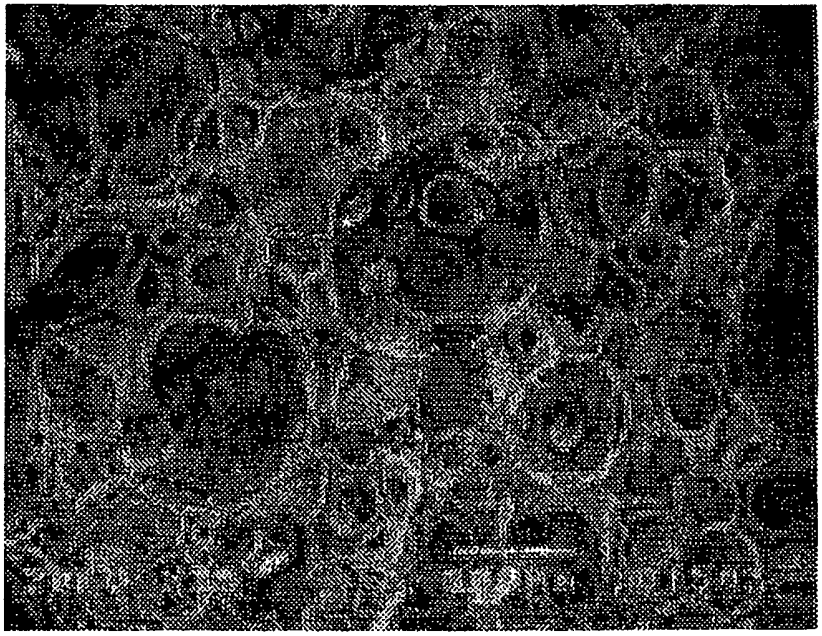

FIG. 16

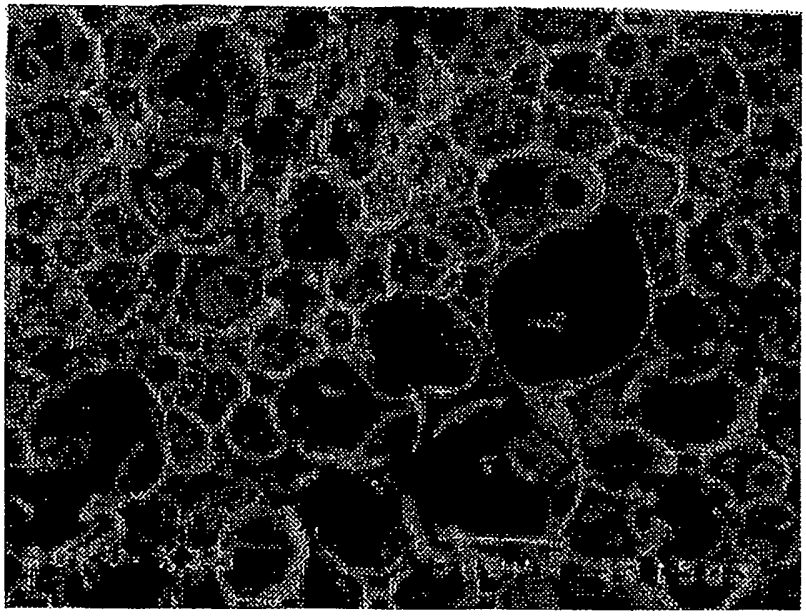

FIG. 17

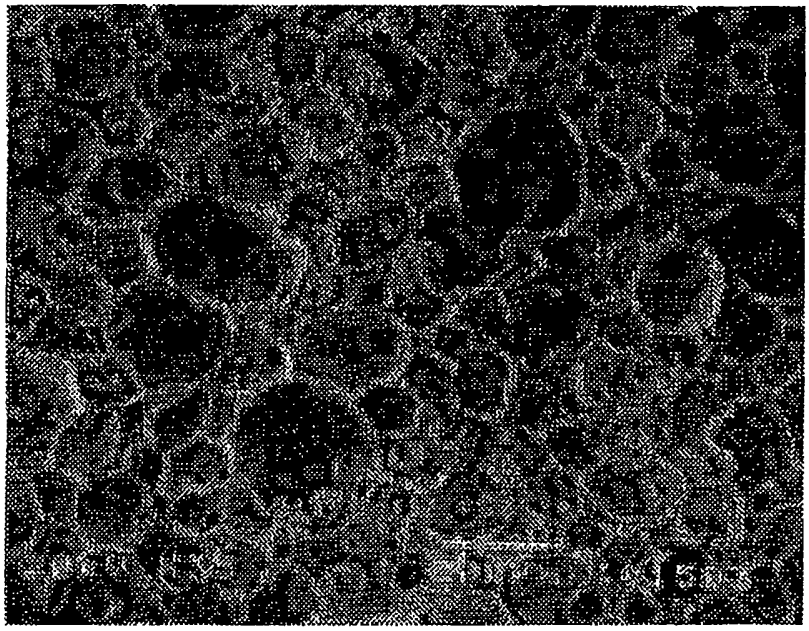

FIG. 18

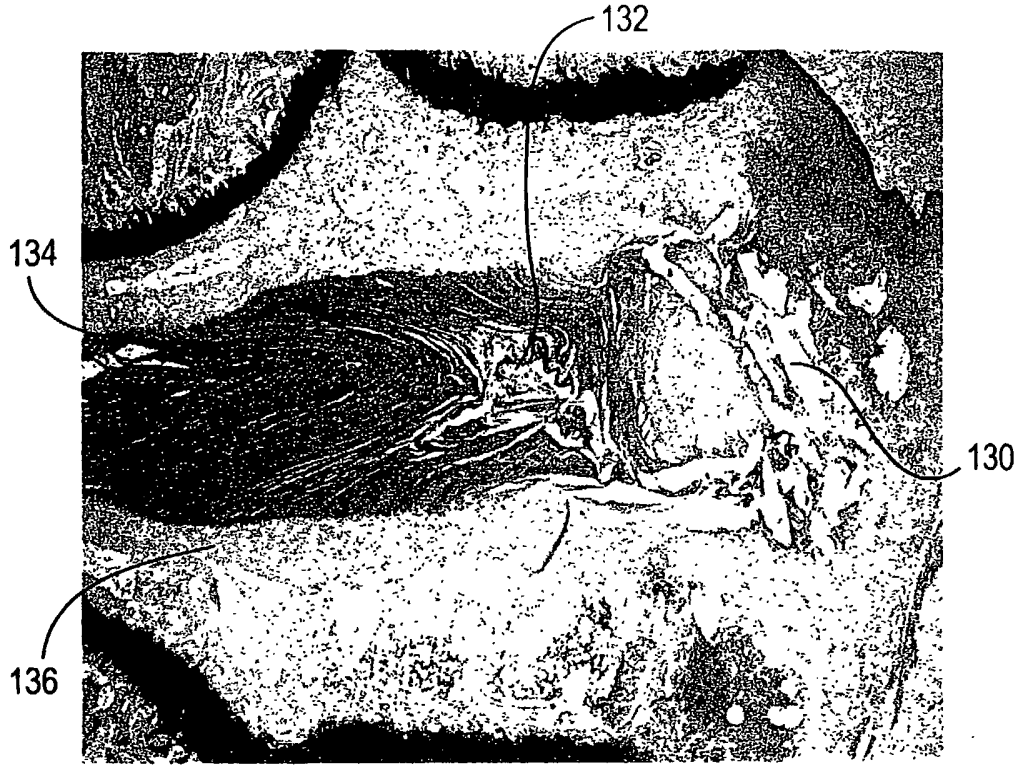

FIG. 19

FIG. 20