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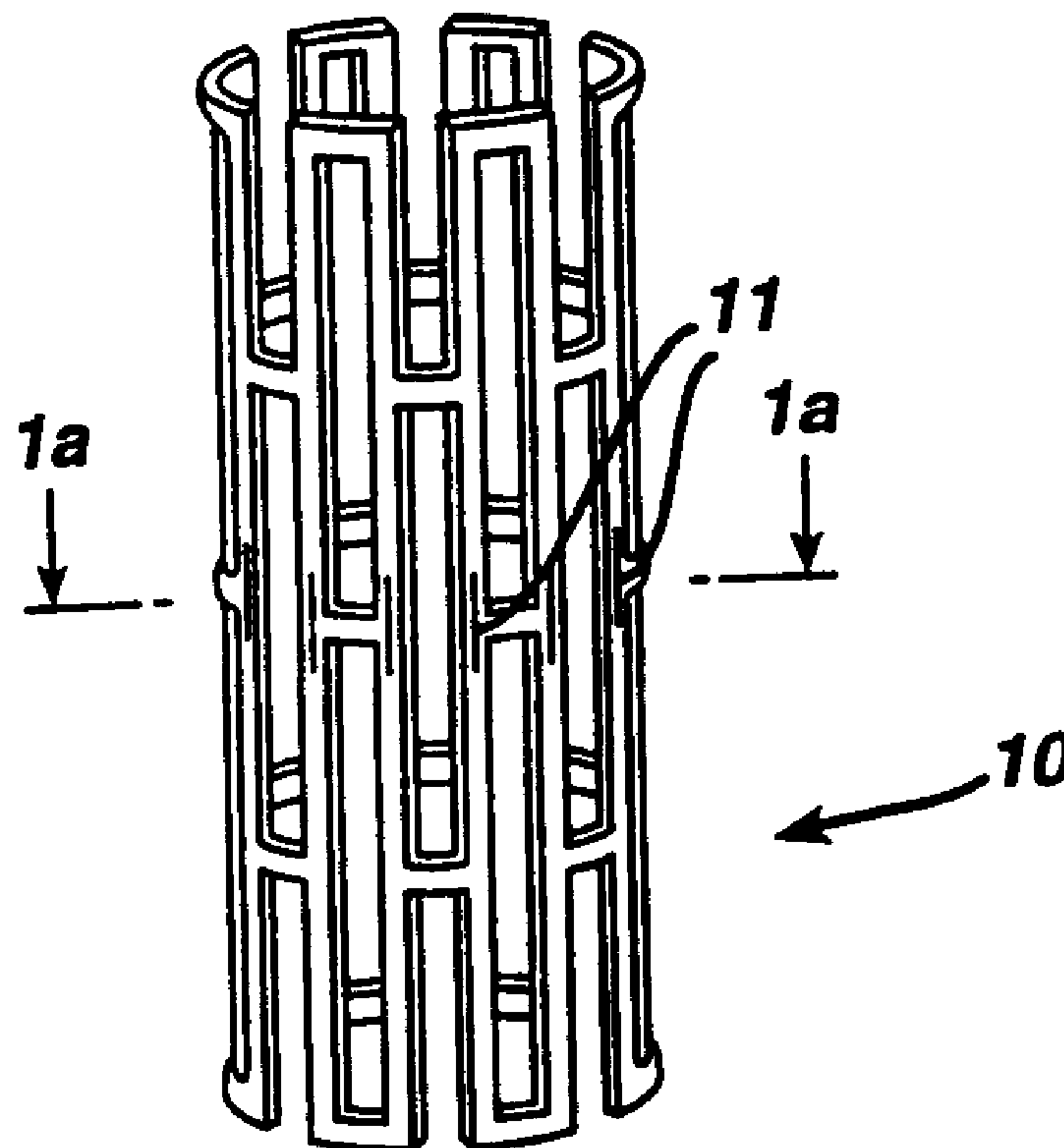
(71) Demandeur/Applicant:
CORDIS CORPORATION, US

(72) Inventeurs/Inventors:
WRIGHT, CAROL, US;
LLANOS, GERARD H., US;
RAKOS, RONALD, US;
KING, KRISTEN, US

(74) Agent: SIM & MCBURNEY

(54) Titre : APPORT LOCAL DE RAPAMYCINE DANS LE TRAITEMENT DES SEQUELLES PROLIFERATIVES
ASSOCIEES AUX PROCEDES ACTP, Y COMPRIS L'APPORT PAR LE BIAIS D'UN TUTEUR MODIFIE

(54) Title: LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED
WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT



(57) Abrégé/Abstract:

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

5

ABSTRACT

10

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

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5 **LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE
 SEQUELAE ASSOCIATED WITH PTCA PROCEDURES,
 INCLUDING DELIVERY USING A MODIFIED STENT**

This application is a Divisional of co-pending Canadian Patent Application No. 2,269,310 dated April 16, 1999.

Field of the Invention:

10 Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also
15 facilitates the performance of the stent in inhibiting restenosis.

Background of the Invention:

20 Re-narrowing (restenosis) of an arteriosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10-50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis
25 are still being determined, our present understanding is that the process of PTCA, besides opening the arteriosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating
30 macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of

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5 intimal SMC and, most significantly, production of large
amounts of extracellular matrix over a period of 3-6
months results in the filling in and narrowing of the
vascular space sufficient to significantly obstruct
coronary blood flow.

0. Several recent experimental approaches to preventing
SMC proliferation have shown promise although the
mechanisms for most agents employed are still unclear.
Heparin is the best known and characterized agent causing
15 inhibition of SMC proliferation both *in vitro* and in
animal models of balloon angioplasty-mediated injury. The
mechanism of SMC inhibition with heparin is still not
known but may be due to any or all of the following: 1)
reduced expression of the growth regulatory protooncogenes
20 c-fos and c-myc, 2) reduced cellular production of tissue
plasminogen activator; are 3) binding and dequstration of
growth regulatory factors such as fibrovalent growth
factor (FGF).

25 Other agents which have demonstrated the ability to
reduce myointimal thickening in animal models of balloon
vascular injury are angiopeptin (a somatostatin analog),
calcium channel blockers, angiotensin converting enzyme
inhibitors (captopril, cilazapril), cyclosporin A,
30 trapidil (an antianginal, antiplatelet agent), terbinafine
(antifungal), colchicine and taxol (antitubulin
antiproliferatives), and c-myc and c-myb antinsense
oligonucleotides.

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5 Additionally, a goat antibody to the SMC mitogen
platelet derived growth factor (PDGF) has been shown to be
effective in reducing myointimal thickening in a rat model
of balloon angioplasty injury, thereby implicating PDGF
directly in the etiology of restenosis. Thus, while no
10 therapy has as yet proven successful clinically in
preventing restenosis after angioplasty, the in vivo
experimental success of several agents known to inhibit
SMC growth suggests that these agents as a class have the
capacity to prevent clinical restenosis and deserve
15 careful evaluation in humans.

Coronary heart disease is the major cause of death in
men over the age of 40 and in women over the age of fifty
20 in the western world. Most coronary artery-related deaths
are due to atherosclerosis. Atherosclerotic lesions which
limit or obstruct coronary blood flow are the major cause
of ischemic heart disease related mortality and result in
500,000-600,000 deaths in the United States annually. To
25 arrest the disease process and prevent the more advanced
disease states in which the cardiac muscle itself is
compromised, direct intervention has been employed via
percutaneous transluminal coronary angioplasty (PTCA) or
coronary artery bypass graft (CABG).

30

PTCA is a procedure in which a small balloon-tipped
catheter is passed down a narrowed coronary artery and
then expanded to re-open the artery. It is currently
performed in approximately 250,000-300,000 patients each

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5 year. The major advantage of this therapy is that
patients in which the procedure is successful need not
undergo the more invasive surgical procedure of coronary
artery bypass graft. A major difficulty with PTCA is the
10 immediately after PTCA (acute reocclusion) and in the long
term (restenosis).

15 The mechanism of acute reocclusion appears to involve
several factors and may result from vascular recoil with
resultant closure of the artery and/or deposition of blood
platelets along the damaged length of the newly opened
blood vessel followed by formation of a fibrin/red blood
cell thrombus. Recently, intravascular stents have been
examined as a means of preventing acute reclosure after
20 PTCA.

25 Restenosis (chronic reclosure) after angioplasty is a
more gradual process than acute reocclusion: 30% of
patients with subtotal lesions and 50% of patients with
chronic total lesions will go on to restenosis after
angioplasty. While the exact mechanism for restenosis is
still under active investigation, the general aspects of
the restenosis process have been identified:

30 In the normal arterial wall, smooth muscle cells
(SMC) proliferate at a low rate (<0.1%/day; ref). SMC in
vessel wall exists in a 'contractile' phenotype
characterized by 80-90% of the cell cytoplasmic volume
occupied with the contractile apparatus. Endoplasmic

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5 reticulum, golgi bodies, and free ribosomes are few and
located in the perinuclear region. Extracellular matrix
surrounds SMC and is rich in heparin-like
glycosylaminoglycans which are believed to be responsible
for maintaining SMC in the contractile phenotypic state.

10

 Upon pressure expansion of an intracoronary balloon
catheter during angioplasty, smooth muscle cells within
the arterial wall become injured. Cell derived growth
factors such as platelet derived growth factor (PDGF),
15 basic fibroblast growth factor (bFGF), epidermal growth
factor (EGF), etc. released from platelets (i.e., PDGF)
adhering to the damaged arterial luminal surface, invading
macrophages and/or leukocytes, or directly from SMC (i.e.,
BFGF) provoke a proliferation and migratory response in
20 medial SMC. These cells undergo a phenotypic change from
the contractile phenotype to a 'synthetic' phenotype
characterized by only few contractile filament bundles but
extensive rough endoplasmic reticulum, golgi and free
ribosomes. Proliferation/migration usually begins within
25 1-2 days post-injury and peaks at 2 days in the media,
rapidly declining thereafter (Campbell et al., In:
Vascular Smooth Muscle Cells in Culture, Campbell, J.H.
and Campbell, G.R., Eds, CRC Press, Boca Ration, 1987, pp.
39-55); Clowes, A.W. and Schwartz, S.M., *Circ. Res.*
30 56:139-145, 1985).

 Finally, daughter synthetic cells migrate to the
intimal layer of arterial smooth muscle and continue to
proliferate. Proliferation and migration continues until

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5 the damaged luminal endothelial layer regenerates at which
time proliferation ceases within the intima, usually
within 7-14 days postinjury. The remaining increase in
intimal thickening which occurs over the next 3-6 months
is due to an increase in extracellular matrix rather than
10 cell number. Thus, SMC migration and proliferation is an
acute response to vessel injury while intimal hyperplasia
is a more chronic response. (Liu et al., Circulation,
79:1374-1387, 1989).

15 Patients with symptomatic reocclusion require either
repeat PTCA or CABG. Because 30-50% of patients
undergoing PTCA will experience restenosis, restenosis has
clearly limited the success of PTCA as a therapeutic
approach to coronary artery disease. Because SMC
20 proliferation and migration are intimately involved with
the pathophysiological response to arterial injury,
prevention of SMC proliferation and migration represents a
target for pharmacological intervention in the prevention
of restenosis.

25 Summary of the Invention:

Novel Features and Applications to Stent Technology

30 Currently, attempts to improve the clinical
performance of stents have involved some variation of
either applying a coating to the metal, attaching a
covering or membrane, or embedding material on the surface
via ion bombardment. A stent designed to include

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5 reservoirs is a new approach which offers several
important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

10 In this application, it is desired to deliver a
therapeutic agent to the site of arterial injury. The
conventional approach has been to incorporate the
therapeutic agent into a polymer material which is then
coated on the stent. The ideal coating material must be
15 able to adhere strongly to the metal stent both before and
after expansion, be capable of retaining the drug at a
sufficient load level to obtain the required dose, be able
to release the drug in a controlled way over a period of
several weeks, and be as thin as possible so as to
20 minimize the increase in profile. In addition, the
coating material should not contribute to any adverse
response by the body (i.e., should be non-thrombogenic,
non-inflammatory, etc.). To date, the ideal coating
material has not been developed for this application.

25 An alternative would be to design the stent to
contain reservoirs which could be loaded with the drug. A
coating or membrane of biocompatible material could be
applied over the reservoirs which would control the
30 diffusion of the drug from the reservoirs to the artery
wall.

One advantage of this system is that the properties
of the coating can be optimized for achieving superior

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5 biocompatibility and adhesion properties, without the
addition requirement of being able to load and release the
drug. The size, shape, position, and number of reservoirs
can be used to control the amount of drug, and therefore
the dose delivered.

10 Description of the Drawings:

The invention will be better understood in connection
with the following figures in which Figures 1 and 1A are
15 top views and section views of a stent containing
reservoirs as described in the present invention;

Figures 2a and 2b are similar views of an alternate
embodiment of the stent with open ends;

20 Figures 3a and 3b are further alternate figures of a
device containing a grooved reservoir; and

Figure 4 is a layout view of a device containing a
25 reservoir as in Figure 3.

Detailed Description of the Invention

Pharmacological attempts to prevent restenosis by
pharmacologic means have thus far been unsuccessful and
30 all involve systemic administration of the trial agents.
Neither aspirin-dipyridamole, ticlopidine, acute heparin
administration, chronic warfarin (6 months) nor
methylprednisolone have been effective in preventing
restenosis although platelet inhibitors have been

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5 effective in preventing acute reocclusion after
angioplasty. The calcium antagonists have also been
unsuccessful in preventing restenosis, although they are
still under study. Other agents currently under study
10 include thromboxane inhibitors, prostacyclin mimetics,
platelet membrane receptor blockers, thrombin inhibitors
and angiotensin converting enzyme inhibitors. These
agents must be given systemically, however, and attainment
of a therapeutically effective dose may not be possible;
antiproliferative (or anti-restenosis) concentrations may
15 exceed the known toxic concentrations of these agents so
that levels sufficient to produce smooth muscle inhibition
may not be reached (Lang et al., 42 Ann. Rev. Med., 127-
132 (1991); Popma et al., 84 Circulation, 1426-1436
(1991)).

20 Additional clinical trials in which the effectiveness
for preventing restenosis of dietary fish oil supplements,
thromboxane receptor antagonists, cholesterol lowering
agents, and serotonin antagonists has been examined have
25 shown either conflicting or negative results so that no
pharmacological agents are as yet clinically available to
prevent post-angioplasty restenosis (Franklin, S.M. and
Faxon, D.P., 4 Coronary Artery Disease, 232-242 (1993);
Serruys, P.W. et al., 88 Circulation, (part 1) 1588-1601,
30 (1993)).

Conversely, stents have proven useful in preventing
reducing the proliferation of restenosis. Stents, such as
the stent 10 seen in layout in Figure 4, balloon-

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5 expandable slotted metal tubes (usually but not limited to
stainless steel), which when expanded within the lumen of
an angioplastied coronary artery, provide structural
support to the arterial wall. This support is helpful in
maintaining an open path for blood flow. In two
10 randomized clinical trials, stents were shown to increase
angiographic success after PTCA, increase the stenosed
blood vessel lumen and to reduce the lesion recurrence at
6 months (Serruys et al., 331 New Eng Jour. Med, 495,
(1994); Fischman et al., 331 New Eng Jour. Med, 496-501
15 (1994). Additionally, in a preliminary trial, heparin
coated stents appear to possess the same benefit of
reduction in stenosis diameter at follow-up as was
observed with non-heparin coated stents. Additionally,
heparin coating appears to have the added benefit of
20 producing a reduction in sub-acute thrombosis after stent
implantation (Serruys et al., 93 Circulation, 412-422,
(1996). Thus, 1) sustained mechanical expansion of a
stenosed coronary artery has been shown to provide some
measure of restenosis prevention, and 2) coating of stents
25 with heparin has demonstrated both the feasibility and the
clinical usefulness of delivering drugs to local, injured
tissue off the surface of the stent.

Numerous agents are being actively studied as
30 antiproliferative agents for use in restenosis and have
shown some activity in experimental animal models. These
include: heparin and heparin fragments (Clowes and
Karnovsky, 265 Nature, 25-626, (1977); Guyton, J.R. et al.
46 Circ. Res., 625-634, (1980); Clowes, A.W. and Clowes,

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5 M.M., 52 Lab. Invest., 611-616, (1985); Clowes, A.W. and
 Clowes, M.M., 58 Circ. Res., 839-845 (1986); Majesky et
 al., 61 Circ Res., 296-300, (1987); Snow et al., 137 Am.
 J. Pathol., 313-330 (1990); Okada, T. et al., 25
 10 Neurosurgery, 92-898, (1989) colchicine (Currier, J.W. et
 al., 80 Circulation, 11-66, (1989), taxol (ref),
 agiotensin converting enzyme (ACE) inhibitors (Powell,
 J.S. et al., 245 Science, 186-188 (1989), angiopeptin
 (Lundergan, C.F. et al., 17 Am. J. Cardiol. (Suppl. B);
 132B-136B (1991), Cyclosporin A (Jonasson, L. et. al., 85
 15 Proc. Nati. Acad. Sci., 2303 (1988), goat-anti-rabbit PDGF
 antibody (Ferns, G.A.A., et al., 253 Science, 1129-1132
 (1991), terbinafine (Nemecek, G.M. et al., 248 J.
 Pharmacol. Exp. Thera., 1167-11747 (1989), trapidil (Liu,
 M.W. et al., 81 Circulation, 1089-1093 (1990), interferon-
 20 gamma (Hansson, G.K. and Holm, 84 J. Circulation, 1266-
 1272 (1991), steroids (Colburn, M.D. et al., 15 J. Vasc.
 Surg., 510-518 (1992), see also Berk, B.C. et al., 17 J.
 Am. Coll. Cardiol., 111B-1 17B (1991), ionizing radiation
 (ref), fusion toxins (ref) antisense oligonucleotides
 25 (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest in rapamycin. Rapamycin is a
 macrolide antibiotic which blocks IL-2- mediated T-cell
 proliferation and possesses antiinflammatory activity.
 30 While the precise mechanism of rapamycin is still under
 active investigation, rapamycin has been shown to prevent
 the G₁ to S phase progression of T-cells through the cell
 cycle by inhibiting specific cell cyclins and cyclin-
 dependent protein kinases (Siekierka, Immunol. Res. 13:

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110-116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al. (Circ Res 76:412-417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al. have shown the rat, porcine, and human SMC migratin can also be inhibited by rapamycin (J Clin Invest 98: 2277-2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., Transplantation 55:1409-1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC

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5 combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

10 Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods:

15

These can vary:

20

- Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.

25

- Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.

30

- or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.

- or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour

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5 deposition methods such as rf-plasma polymerization) and combinations thereof.

- Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake

10

- Extravascular delivery by the pericardial route

- Extravascular delivery by the advential application of sustained release formulations.

15

Uses: for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.

prevention of tumor expansion from stents

prevent ingrowth of tissue into catheters and

20

shunts inducing their failure.

1. Experimental Stent Delivery Method - Delivery from Polymer Matrix:

25

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolacton-glycolide, polyorthoesters, polyanhydrides; poly-aminoacids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends

30

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5 thereof. Nonabsorbable biocompatible polymers are also
suitable candidates. Polymers such as polydimethyl-
siloxane; poly(ethylene-vinylacetate); acrylate based
polymers or copolymers, e.g., poly(hydroxyethyl
methacrylate, polyvinyl pyrrolidinone; fluorinated
10 polymers such as polytetrafluoroethylene; cellulose
esters.

Polymer/drug mixture is applied to the surfaces of
the stent by either dip-coating, or spray coating, or
15 brush coating or dip/spin coating or combinations thereof,
and the solvent allowed to evaporate to leave a film with
entrapped rapamycin.

2. Experimental Stent Delivery Method - Delivery from
20 Microporous Depots in Stent Through a Polymer Membrane
Coating:

Stent, whose body has been modified to contain
micropores or channels is dipped into a solution of
25 Rapamycin, range 0.001 wt% to saturated, in organic
solvent such as acetone or methylene chloride, for
sufficient time to allow solution to permeate into the
pores. (The dipping solution can also be compressed to
improve the loading efficiency.) After solvent has been
30 allowed to evaporate, the stent is dipped briefly in fresh
solvent to remove excess surface bound drug. A solution
of polymer, chosen from any identified in the first
experimental method, is applied to the stent as detailed

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above. This outerlayer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method - Delivery via lysis of a Covalent Drug Tether

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method - Pericardial Delivery

A: Polymeric Sheet Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-glycolide) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10 μ to 1000 μ . The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating: Rapamycin is combined with a polymer that has a melting temperature just above 37°C, range 40°-45°C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformally to the

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vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in Figures 1a, 2a and 3a, any stent strut 10, 20, 30 can be modified to have a certain reservoir or channel 11, 21, 31, which may be laser cut into the strut. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. Figure 4 shows a stent 40 with a reservoir 45 created at the apex of a flexible strut. Of course, this reservoir 45 is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will be disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be

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5 perceived to fall within the scope of the invention which
is to be realized from the attached claims and their
equivalents.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS

1. A stent containing a polymer and rapamycin or its analogs wherein said rapamycin or its analogs are contained in a therapeutically beneficial amount to combat restenosis, said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said rapamycin or its analogs applied to said strut, and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a reservoir of said rapamycin containing coating applied therein.

2. A stent comprising:

a generally thin walled cylinder, said cylinder containing a plurality of struts, said struts expandable struts having a generally uniform thickness; and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a therapeutic agent applied therein and wherein the therapeutic agent is rapamycin.

3. A stent comprising:

a generally thin walled cylinder, said cylinder containing a plurality of struts, said struts expandable dependent on the amount of force applied to said strut, and said struts having a generally uniform thickness; and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open

top, and said channel smaller in all dimensions than said strut, said channel containing a therapeutic agent applied therein; and

wherein said channel has a generally rectangular perimeter.

4. In combination:

a stent comprising:

a generally thin walled cylinder, said cylinder containing a plurality of struts, said struts expandable dependent on the amount of force applied to said strut, and said struts having a generally uniform thickness; and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a therapeutic agent applied therein; and

wherein said channel has a generally rectangular perimeter; and

wherein said therapeutic agent is rapamycin coated to said channel.

5. The stent of claim 4 wherein said channel is rectangular in shape.

6. The combination of claim 5 wherein said channel is laser cut into said strut.

7. A stent comprising a generally thin walled structure containing a plurality of struts, the struts expandable to assume the shape of a lumen into which the stent is emplaced, said struts having a thickness, and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said

channel smaller in all dimensions than said strut, said channel containing a therapeutic agent applied therein and wherein the therapeutic agent is rapamycin.

8. A stent comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said struts expandable dependent on the amount of force applied to said strut, and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a reservoir of a therapeutic agent applied therein.

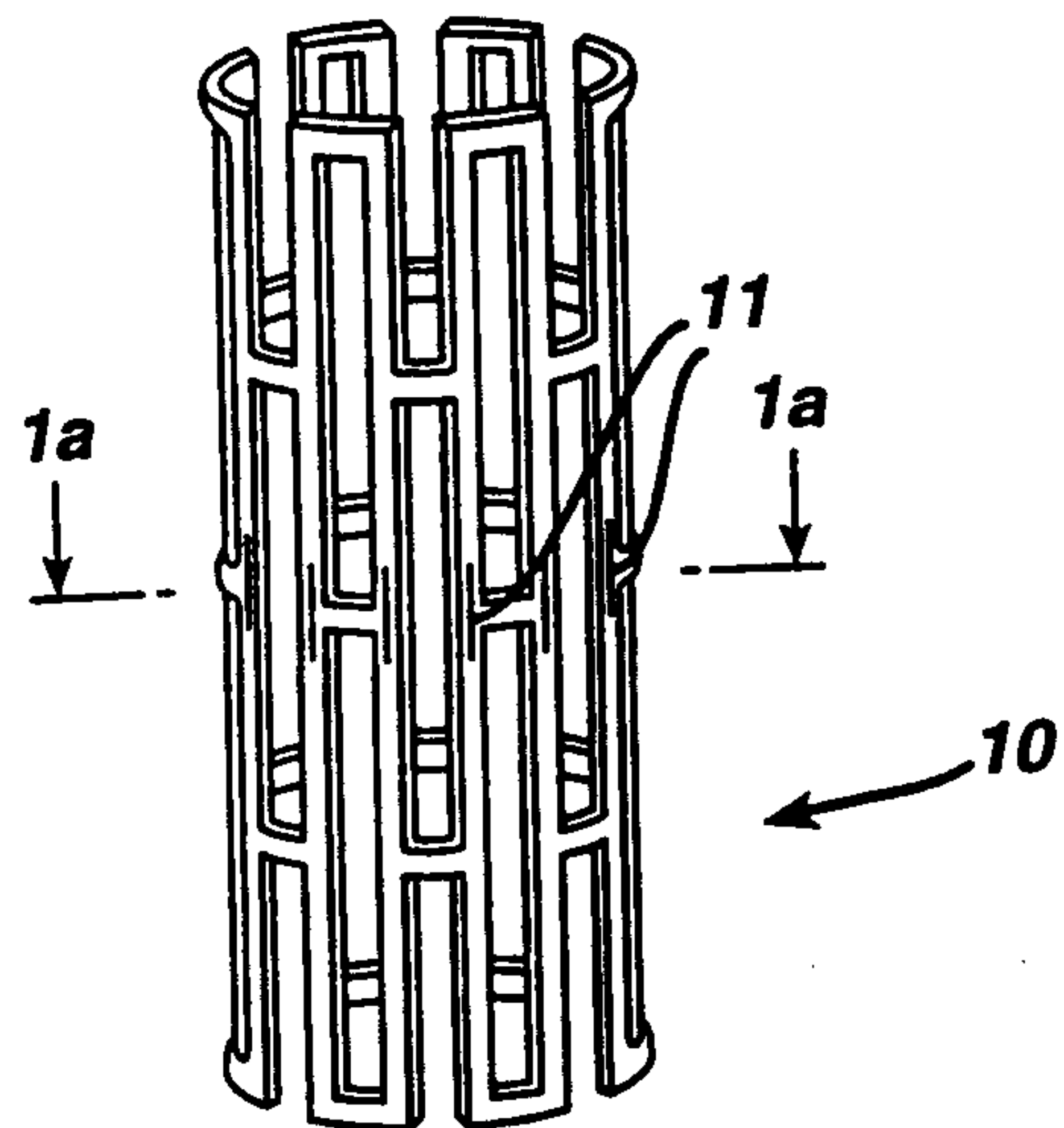
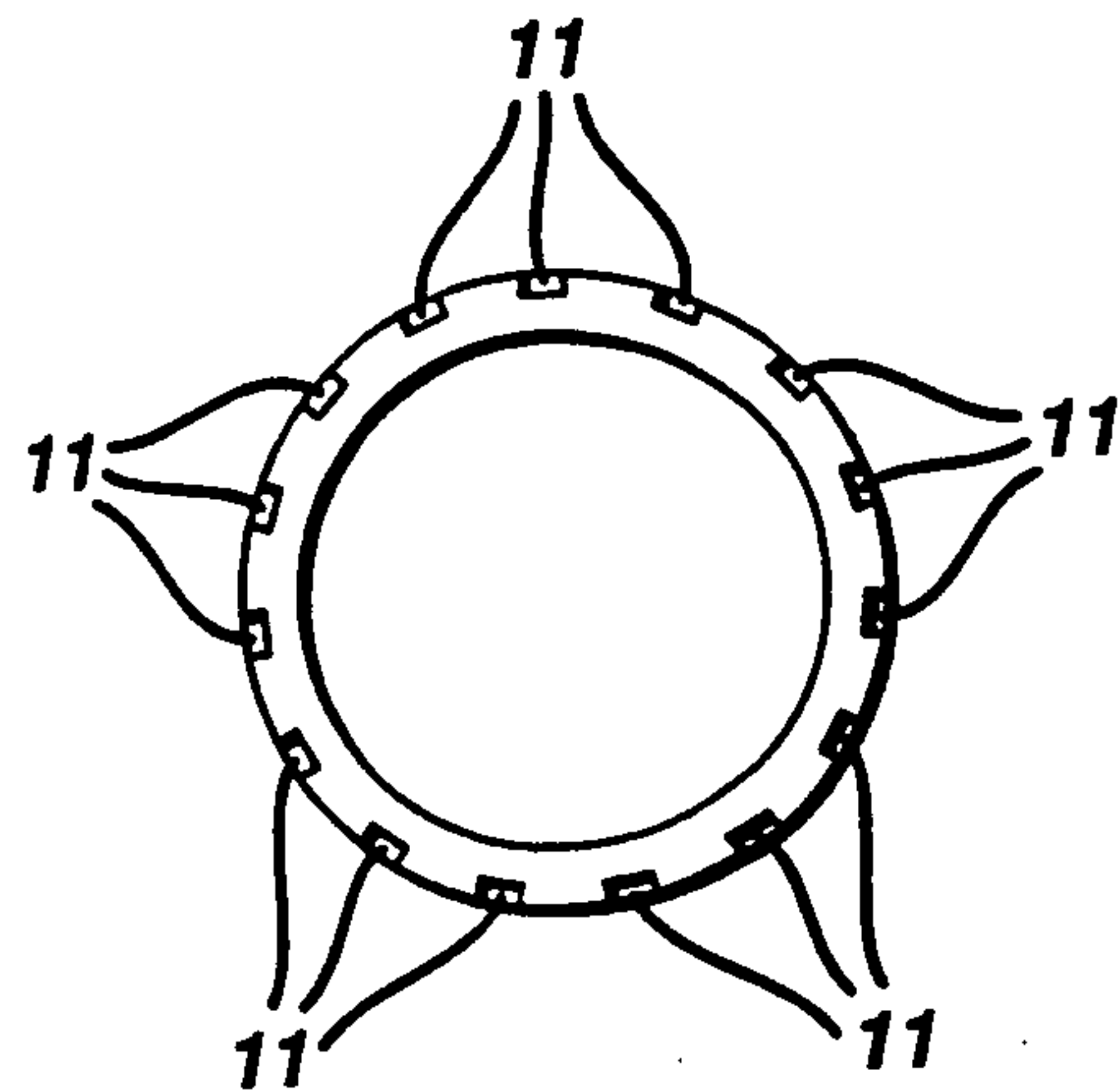
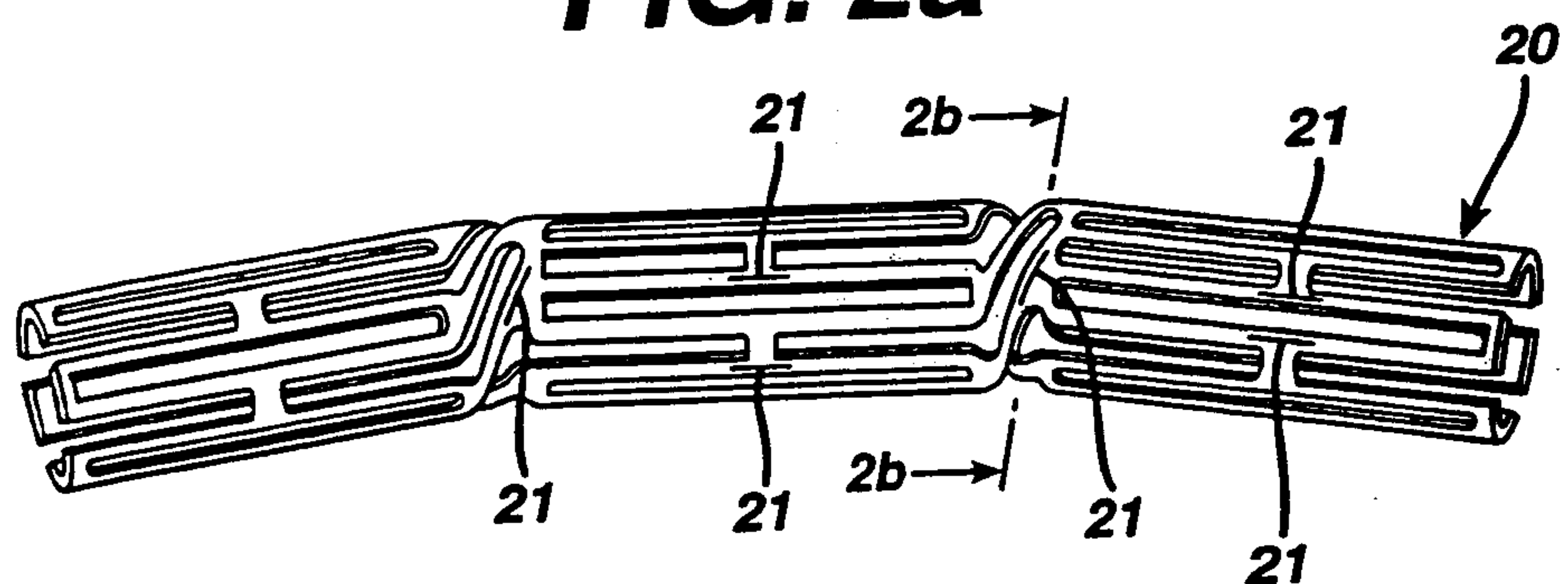
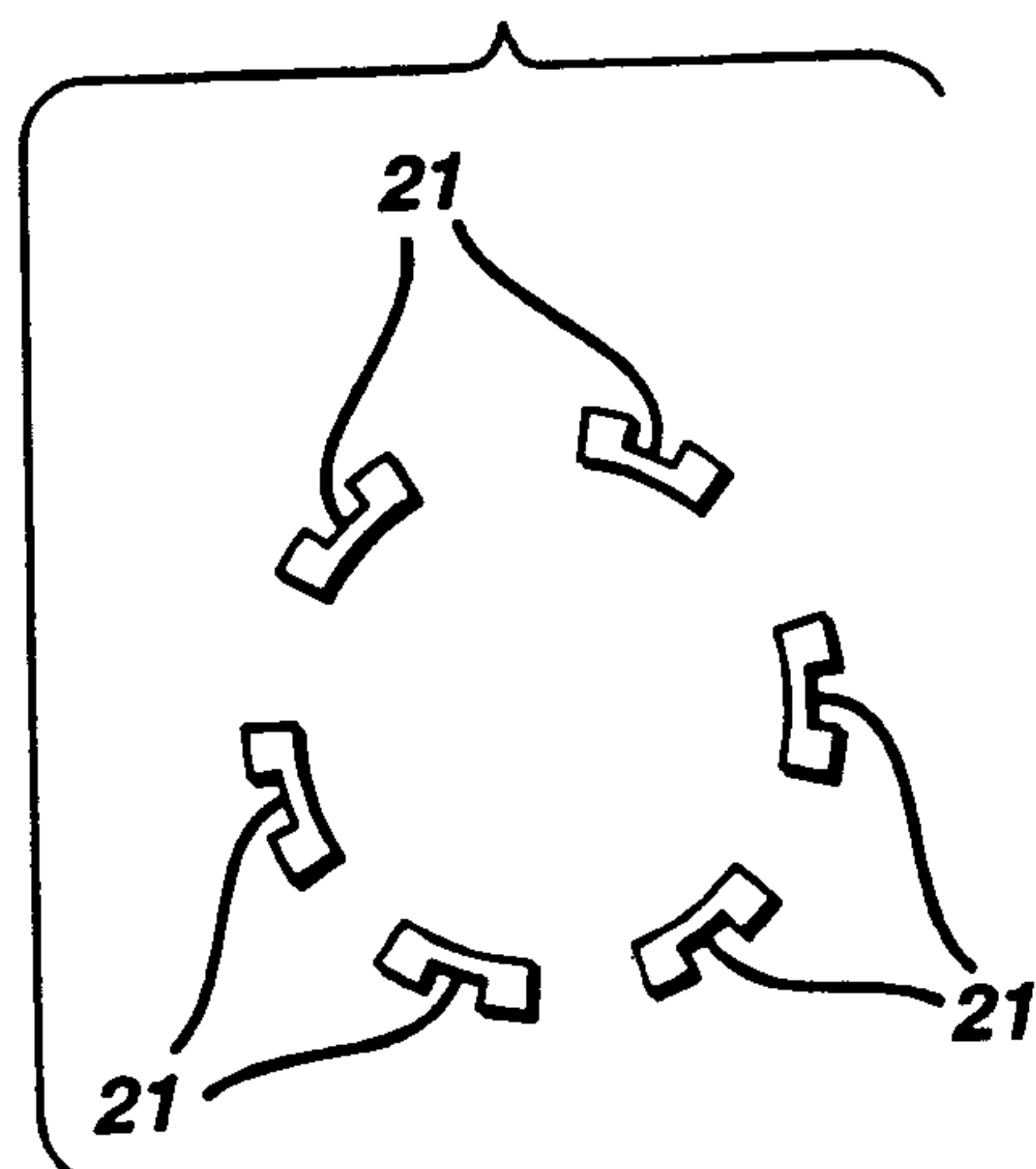
FIG. 1**FIG. 1a****FIG. 2a****FIG. 2b**

FIG. 3a

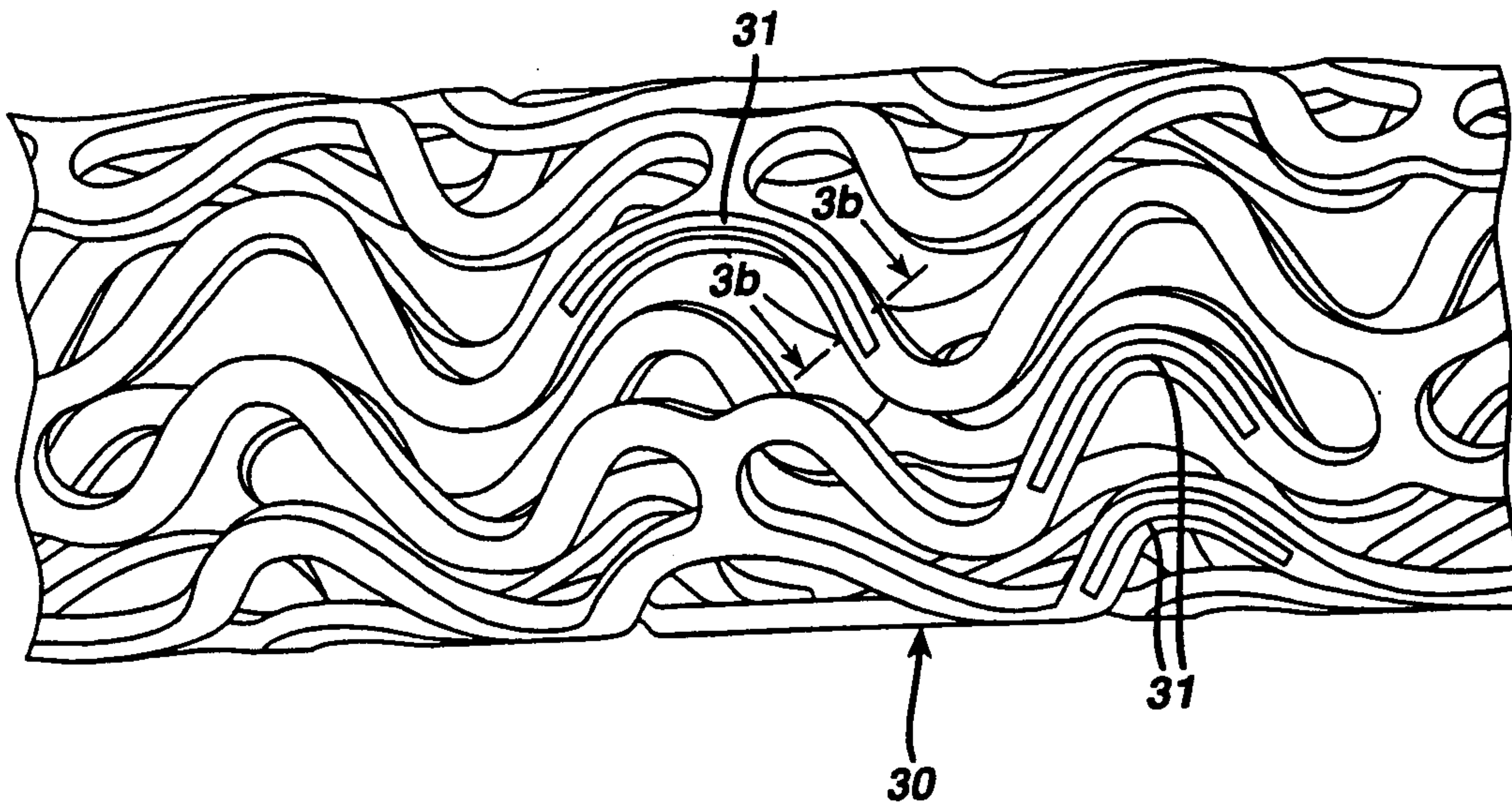


FIG. 3b

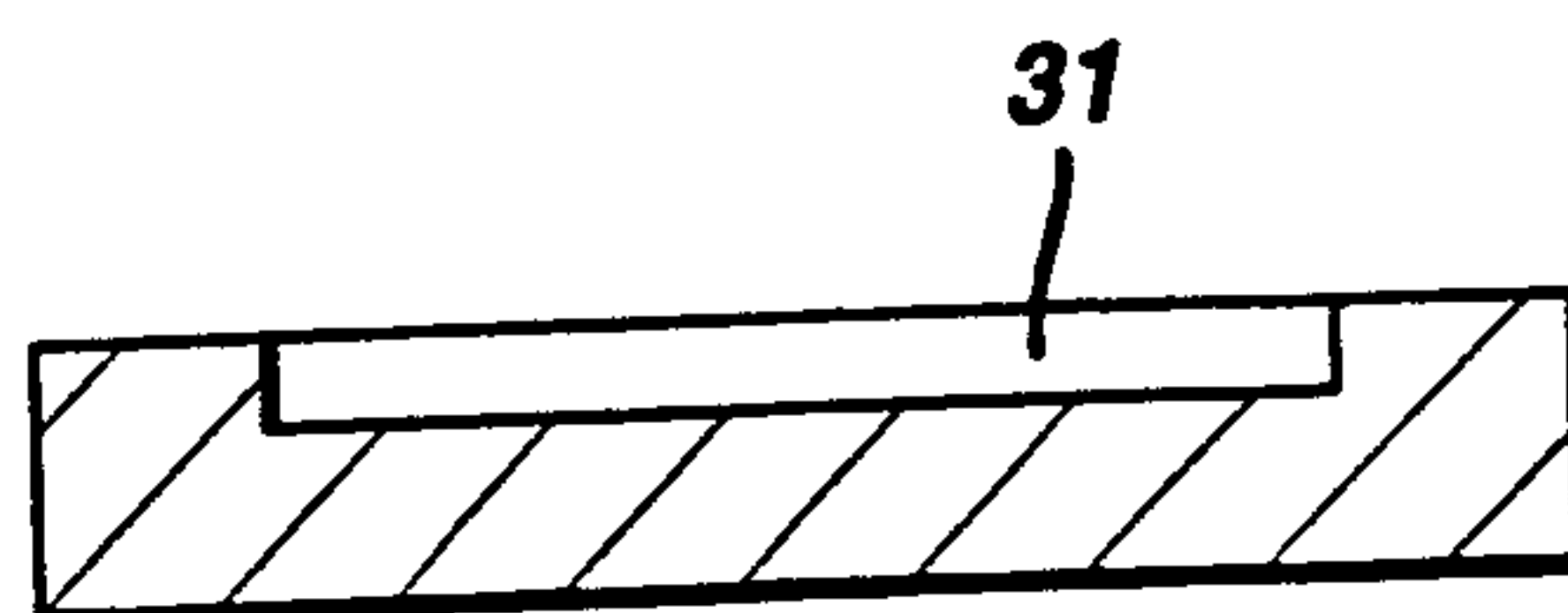


FIG. 4

