

(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 2005214040 B2**

- (54) Title
Methods and apparatus for intraocular brachytherapy
- (51) International Patent Classification(s)
A61N 5/00 (2006.01) **A61N 5/10** (2006.01)
- (21) Application No: **2005214040** (22) Date of Filing: **2005.02.11**
- (87) WIPO No: **WO05/079294**
- (30) Priority Data
- (31) Number (32) Date (33) Country
60/544,001 **2004.02.12** **US**
- (43) Publication Date: **2005.09.01**
(44) Accepted Journal Date: **2011.03.31**
- (71) Applicant(s)
Neo Vista, Inc.
- (72) Inventor(s)
Behrmann, Sabine;De Juan, Eugene;Phillipps, Gerd T.;Pintaske, Rainer;Hillstead, Richard;Fritz, Eberhard;Trip, Roelof;Humayun, Mark;Larsen, Charles
- (74) Agent / Attorney
Peter Maxwell & Associates, Level 6 60 Pitt Street, Sydney, NSW, 2000
- (56) Related Art
US 2002/0115902
US 6004279
US 6443881
US 5637073
US 6676590

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
1 September 2005 (01.09.2005)

PCT

(10) International Publication Number
WO 2005/079294 A2

(51) International Patent Classification: Not classified

PHILLIPPS, Gerd, T. [DE/DE]; Gartenstr. 1b, 14169 Berlin (DE).

(21) International Application Number:
PCT/US2005/004391

(74) Agents: MC FARRON, Gary, W. et al.; Cook, Alex, McFarron, Manzo, Cummings & Mehler, Lt, d., 200 West Adams Street, Suite 2850, Chicago, IL 60606 (US).

(22) International Filing Date: 11 February 2005 (11.02.2005)

(25) Filing Language: English

(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.

(26) Publication Language: English

(30) Priority Data:
60/544,001 12 February 2004 (12.02.2004) US

(71) Applicant (for all designated States except US): NEO VISTA, INC. [US/US]; 2750 Premier Parkway, Suite 200, Duluth, GA 30097 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): HILLSTEAD, Richard [US/US]; 3495 Leaf Land Court, Duluth, GA 30097 (US). LARSEN, Charles [US/US]; 6080 Cherokee Trace, Cumming, GA 30131 (US). TRIP, Roelof [US/US]; 3317 Rae Place, Lawrenceville, GA 30044 (US). PINTASKE, Rainer [DE/DE]; c/o STEP Sensortechnik und Elektronik Pockau GmbH, Siedlungsstrasse 5-7, 09509 Pockau (DE). BEHRMANN, Sabine [DE/DE]; Sulinger Strasse 39, 27305 Bruchhausen-Vilsen (DE). FRITZ, Eberhard [DE/DE]; c/o AEA Technology QSA GmbH, Gieselweg 1, 38110 Braunschweig (DE). DE JUAN, Eugene [US/US]; 3707 Via Serrano, La Canada Flintridge, CA 91011 (US). HUMAYUN, Mark [US/US]; 2757 Sleepy Hollow Place, Glendale, CA 91206 (US).

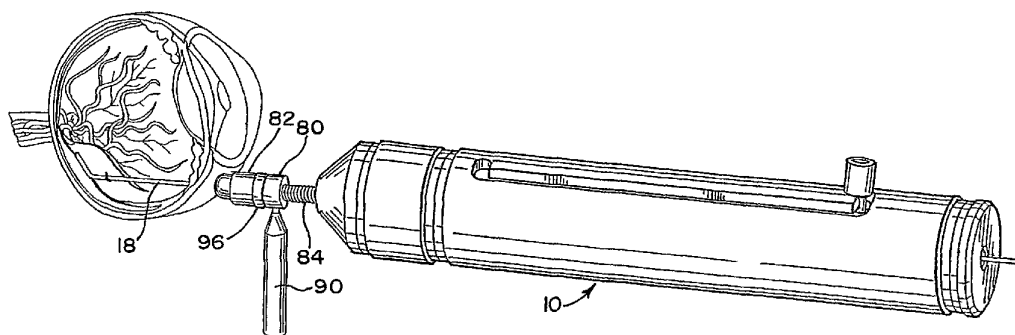
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, 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).

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: METHODS AND APPARATUS FOR INTRAOCULAR BRACHYTHERAPY



(57) Abstract: A method for performing intraocular brachytherapy and an apparatus for performing the same is disclosed. The apparatus preferably comprises a hand-held delivery device that advances a radiation source into an associated cannula or probe that is positioned adjacent the target tissue. The handpiece provides for shielded storage of the radiation source when retracted from the cannula and includes a slider mechanism for advancing and retracting the radiation source. The radiation source is mounted to a wire that has a flexible distal end and a relatively stiffer proximal end. A positioning system for the cannula is also disclosed.

METHODS AND APPARATUS FOR INTRAOCULAR BRACHYTHERAPY

[0001] The present invention relates to apparatus, systems and methods for performing intraocular brachytherapy. The invention may be employed in the treatment of a variety of eye disorders, but is particularly suited for treatment of macular degeneration in which neovascularized ocular tissue is treated by means a of local, directional delivery of a radiation dose emitted by a radioactive source to target tissues.

BACKGROUND

[0002] The slow, progressive loss of central vision is known as macular degeneration. Macular degeneration affects the macula, a small portion of the retina. The retina is a fine layer of light-sensing nerve cells that covers the inside back portion of the eye. The macula is the central, posterior part of the retina and contains the largest concentration of photoreceptors. The macula is typically 5 to 6 mm in diameter, and its central portion is known as the fovea. While all parts of the retina contribute to sight, the macula provides the sharp, central vision that is required to see objects clearly and for daily activities including reading and driving.

[0003] Macular degeneration is generally caused by age (termed Age Related Macular Degeneration or "AMD") or poor circulation in the eyes. Smokers and individuals with circulatory problems have an increased risk for developing the condition. AMD is the leading cause of blindness in people older than 50 years in developed countries. Between the ages of 52-64, approximately 2% of the population are affected. This rises to an astounding 28% of the population over the age of 75.

[0004] There are two forms of macular degeneration, which are known as "wet" and "dry" macular degeneration. Dry macular degeneration blurs the central vision slowly over time. Individuals with this form of macular degeneration may experience a dimming or distortion of vision that is particularly noticeable when trying to read. In dry macular

degeneration, yellowish deposits called drusen develop beneath the macula. Drusen are accumulations of fatty deposits, and most individuals older than 50 years have at least one small druse. These fatty deposits are usually carried away by blood vessels that transport nutrients to the retina. However, this process is diminished in macular degeneration and the deposits build up. Dry macular degeneration may also result when the layer of light-sensitive cells in the macula become thinner as cells break down over time. Generally, a person with the dry form of macular degeneration in one eye eventually develops visual problems in both eyes. However, dry macular degeneration rarely causes total loss of reading vision.

[0005] Wet macular degeneration (which is the neovascular form of the disease) is more severe than dry macular degeneration. The loss of vision due to wet macular degeneration also comes much more quickly than dry macular degeneration. In this form of the disease, unwanted new blood vessels grow beneath the macula (Choroidal Neo-Vascularization (CNV) endothelial cells). These choroidal blood vessels are fragile and leak fluid and blood, which causes separation of tissues and damages light sensitive cells in the retina. Individuals with this form of macular degeneration typically experience noticeable distortion of vision such as, for example, seeing straight lines as wavy, and seeing blank spots in their field of vision.

[0006] Early diagnosis of the wet form of macular degeneration is vital. If the leakage and bleeding from the choroidal blood vessels is allowed to continue, much of the nerve tissue in the macula may be killed or damaged. Such damage cannot be repaired because the nerve cells of the macula do not grow back once they have been destroyed. While wet AMD comprises only about 20% of the total AMD cases, it is responsible for approximately 90% of vision loss attributable to AMD.

[0007] It has been proposed to provide a device that is particularly suitable for the localized delivery of radiation

for the treatment of macular degeneration. See, U.S. Pub. Appln. US 2002/0115902A1 to DeJuan, et al., which is incorporated herein by reference. A localized retinal detachment (called a "bleb") is created by performing a retinotomy and injecting saline therethrough using a subretinal infusion needle, thus creating a space between the partially-detached retina and the area of chloridal neo-vascularization. A radiation-emitting source is introduced into the bleb and the CNV is directly irradiated. The exposure of the new blood vessels formed during the wet form of macular degeneration to radiation provides sufficient disruption of the cellular structures of the new blood cell lesions to reverse, prevent, or minimize the progression of the macular degeneration disease process. Such therapy can potentially restore visual acuity, extend retention of visual acuity or slow the progressive loss of visual acuity.

[0008] The present application relates to advances in apparatus, systems and methods for performing intraocular brachytherapy, in general, and for the treatment of macular degeneration with radiation, in particular.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] Fig. 1 is a partial longitudinal cross-sectional view of an apparatus for performing intraocular brachytherapy comprising a handpiece, a cannula secured to the handpiece, and a radiation source wire ("RSW") interior of the handpiece and cannula in a retracted position.

[00010] Fig. 2 is a cross-sectional view of the apparatus of Fig. 1 with the radiation-emitting element advanced to the treatment position.

[00011] Fig. 3 is a top view (as compared to Figs. 1 and 2) of a portion of the housing comprising part of handpiece shown in Fig. 1.

[00012] Fig. 4 is an enlarged view of the cannula associated with the system of Fig. 1, in partial cross-section.

[00013] Fig. 5 is a fragmentary, cross-sectional view of the radioactive source wire forming a portion of the system shown in

Fig. 1.

[00014] Fig. 6 is a perspective view of the distal end of the cannula and a dose flattening filter comprising a portion of the tip or distal end of the cannula.

[00015] Fig. 7 is an exploded perspective view of a first embodiment of a positioning system for use with the system of Fig. 1.

[00016] Figs. 8 and 9 illustrate the use of the positioning system of Fig. 7 in connection with the system of Fig. 1.

[00017] Fig. 10 is an enlarged view showing the treatment of CNV with the device of Fig. 1.

[00018] Fig. 11 shows the dose rate profile at the treatment side of the delivery device.

[00019] Fig. 12 is a schematic view of a further version of the cannula for use in the present invention having an inflatable balloon at its distal end.

[00020] Fig. 13 is a schematic view of an alternate embodiment of the cannula of Fig. 1 including retractable wires for properly spacing the treatment end of the cannula and the radioactive source from the target tissue.

[00021] Fig. 14 is a schematic view of an alternate version of the cannula in which a retractable wire basket is provided for maintaining the proper spacing of the radiation source with respect to the target tissue.

[00022] Fig. 15 is a schematic view of a further embodiment of the cannula for use with the present invention in which the cannula includes a lumen for injecting and withdrawing various fluids at the location of the distal end of the cannula.

[00023] Fig. 16 is a cross-sectional view of the cannula of Fig. 15.

[00024] Fig. 17 is a schematic view of a further embodiment of the cannula for use in connection with the present invention in which the non-treatment side of the distal end of the catheter is relieved to minimize contact with the retina.

DETAILED DESCRIPTION

[00025] In the sub-retinal treatment of AMD, vitreoretinal

surgical techniques are used to facilitate placement of a radioactive source that preferably, but not exclusively, emits beta or other ionizing radiation temporarily in a subretinal space by means of an intraocular cannula, sheath or probe. Other non-ionizing radiation sources, such as light or heat sources, as circumstances require, may also be used.

[00026] In accordance with one aspect of the present invention, an apparatus is provided employing the radioactive source and a delivery device that permits movement of the source between a stored position and treating position. When in the stored (retracted) position, the radiation source is surrounded by a suitable material, such as a stainless steel and lead lining, that effectively protects the surgeon and patient during handling and initial positioning. During treatment, the source is preferably located within a specially designed tip of platinum iridium (Pt/Ir), or other suitable material, that provides for directional administration of the radiation with controlled intensity, while shielding and protecting the retina and other surrounding non-target tissues.

[00027] With reference to Figs. 1 and 2, the system, generally designated 10, includes two main components: a radiation source, which may be located at the distal end of a source wire (RSW) 12 and a delivery device 14 that comprises, in the illustrated embodiment, a handle 16 and a delivery cannula 18 (also called a sheath or probe). In addition, a positioning system 20, shown in Fig. 7, and method, illustrated in Figs. 8 and 9, are provided to assist in the precise positioning of the device within the eye.

[00028] Radiation source is broadly defined herein, and is not limited to ionizing radiation, light radiation, or heat radiation. For example, the radiation source is intended to include a treatment source of any of a variety of treatment regimens, including ionizing radiation. The radiation source for the RSW 12 comprises any suitable radiation source, including radioactive materials such as gamma and beta emitters, x-ray (e.g., miniaturized x-ray generators), and non-ionizing

radiation sources, such as laser or other light sources. Alternatively, ultrasound, heat, cryo-ablation, or microwave sources may also be utilized.

[00029] Preferably, an essentially beta emitting material, such as a Strontium/Yttrium 90 (Sr-90/Y-90) beta emitting isotope is used. With a source activity of approximately 11 mCi and a location of about 1-3 mm from the target tissue (preferably about 1-1.5 mm), the treatment duration is relatively short, approximately 2-4 minutes. The system and method provide for sub-retinal delivery of radiation at the site of the choroidal neovascularization that occurs in macular degeneration, or other treatment site. When employing ionizing radiation, the system preferably provides radiation to a target site at a dose rate of from approximately 4 to 20 GY/min; with a preferred target dose of between approximately 10 and 40 GY, with the target dose more preferably being approximately 26 GY for neovascularized tissue.

[00030] As illustrated in Fig. 5, the preferred embodiment of the radiation source includes a cylindrical aluminum insert 22 that is doped with the Sr-90/Y-90 isotope in accordance with conventional techniques and preferably resides inside a sealed stainless steel canister. The canister comprises a seed tubing 24 sealed on its distal end with a lid 26 and on its proximal end with a lid 28. The stainless steel canister may be mounted to a solid or braided wire made of stainless steel (or other material) to form the RSW 12 that is used to advance the source to and retract the source from the treatment location.

[00031] As shown in Fig. 5, the radioactive source wire 12 preferably includes a relatively flexible distal or leading strand 30 and a relatively stiffer proximal or handle strand 32. Specifically, the flexibility of the leading strand 30 is such as to allow unimpeded mechanical transport through the cannula 18 around a radius of curvature of from 4 to 8 mm. The RSW 12 has an overall length on the order of 190 mm, which provides a 10mm-15mm protrusion of the wire from the rear of the handle 16 (as seen in Figs. 1 and 2) when the RSW 12 is advanced to the

treatment position, thus providing for removal or repositioning of the RSW, if necessary.

[00032] The distal end of the leading strand 30 includes a connection tubing 34 closed by a lid 36 for facilitating attachment of the canister housing the radioactive insert 22. A further connection tubing 38 is used to join the proximal end of the leading strand 30 to the distal end of the handle strand 32. In the illustrated embodiment, the leading strand 30 has a smaller outside diameter than the handle strand. Thus, the proximal end of the leading strand 30 carries an additional length of tubing 40 to build up the outside diameter of the leading strand 30 to match that of the handle strand. The proximal end of the handle strand 32 also includes a length of tubing 41 for reinforcement. Other than the radioactive insert 22, the various components of the RSW 12 are preferably made of stainless steel and are joined together by laser welding. Other means for delivering and/or retrieving the radioactive source, as disclosed in the prior art, may also be used. For example, the radioactive source may not be secured to a wire, and movement of the source between treatment and storage positions can be accomplished pneumatically or hydraulically. See, e.g., U.S. Patent No. 5,683,345, which is incorporated herein by reference.

[00033] The delivery device 14 is preferably, but not necessarily, handheld to facilitate control and positioning of the delivery cannula 18 during use. When not in use, the radiation source 22, e.g., a beta radiation source, may be positioned inside the shielded storage handle 16. The handle 16 includes a slider mechanism to which a proximal portion of the RSW 12 is secured, the slide mechanism being moveable between treatment position (Fig. 2), in which the radioactive source 22 is positioned at the distal end of the cannula 18, and a retracted position (Fig. 1) for storage of the radioactive source 22 within the handle 16. While in the storage position, the radiation source is preferably shielded by a combination of stainless steel (inner shield) and lead (outer shield). The

stainless steel shield blocks the beta radiation, while the lead shield reduces the secondary radiation (known as brehmsstrahlung). Other suitable materials may also be used for shielding.

[00034] With reference to Figs. 1-3, the handle 16 comprises a multi-part housing with an elongated cylindrical case 42 closed at its proximal end by end cap 44 and at its distal end by a central hub 46, to which the cannula 18 is secured. The hub 46 is preferably made of stainless steel and serves as the inner radiation shield for the radioactive source when in the storage position. The wall thickness of the shielding portion of the hub is approximately 1.9 mm. The hub 46 also carries the lead outer shield, designated 48, which has a wall thickness of approximately 4.6 mm. The hub 46 and outer shield 48 are carried by a cup-like member 50 that is secured to the distal end of the case 42.

[00035] As noted above, the handle 16 includes an advancement or positioning mechanism (also referred to as a slider mechanism), generally designated 52, for moving the radioactive source 22 between the storage and treatment positions. The slider mechanism 52 includes a carrier member 54 that is slidably received on the interior of the cylindrical case 42 of the handle 16. The carrier 54 includes a central aperture, through which the handle strand 32 of the RSW 12 extends, with the RSW 12 being secured to the carrier 54 by means of a set screw 56.

[00036] For moving the carrier 54 between the proximal and distal ends of the case 42, an actuator pin 58 that extends through an elongated slot 60 in the case 42 is secured to the carrier 54. As illustrated, the slot 60 lies in a plane defined by the curved cannula 18, thus having the same orientation as the cannula curve. The slot 60 permits approximately 60 mm, or less, of travel for the carrier 54 and includes offsets 62, 64 at its distal and proximal ends, respectively, for receiving the actuator pin 58, thus providing positive visual and tactile indications of the radioactive source 22 being located in the

treatment and storage positions. The proximal side of the carrier 54 also includes a coil spring 66 secured thereto by screw 68 for biasing the actuator pin into a locked condition within proximal offset 64 when in the retracted position.

[00037] With reference to Fig. 4, the intraocular probe 18 is preferably an integral part of the delivery device, and is fabricated of a rigid material, such as stainless steel. The probe, or cannula, in the illustrated embodiment, comprises a single lumen and is sealed at the distal end to prevent contact between the radiation source and the patient or the patient's bodily fluids. More particularly, the distal end of the probe includes an inner sleeve 70 (best seen in Fig. 6) in which the radiation source is located when in the treatment position. The inner sleeve 70 is configured to provide a desired dose profile, which is discussed in greater detail below. The inner sleeve 70 is received in a cover sleeve 72 that serves to seal the inner sleeve 70 and also provides some radiation attenuation.

[00038] The distal end of the cannula 18 is curved or bent at an angle to facilitate proper alignment of the radiation source and the treatment area. The tip 74 of the probe 18 also preferably has a rounded wedge shape to facilitate positioning of the distal end under the retina, when the retina is partially detached and raised to form a "bleb" (as by injection of saline or other liquid under the retina) during the performance of the method.

[00039] The treatment side of the tip includes a molded, machined or otherwise formed window 76 (sealed by the cover sleeve 72) that allows for directional administration of radiation. The window 76 is subdivided into four smaller windows by longitudinal and transverse splines 77 that intersect at centrally located solid area 79 that acts as a flattening filter to reduce the peak radiation from the source 22 received by tissue closest to the radiation source. As a result, the tissue to be irradiated at the treatment site receives a more uniform dosage. This flattening effect is shown in Fig. 11, which plots the dose rate (in GY/min) as a function of radial

and axial distance from the radiation source center. As can be seen in Fig. 11, the peak dose rate is generally flat at the center of the source, and decreases essentially linearly as the distance from the center increases. Various structures of the flattening filter are discussed in the co-pending PCT application "Radioactive Radiation Source for Ophthalmic Brachytherapy," PCT/EP2004/012415, filed November 3, 2004, which is incorporated herein by reference. In general, the flattening filter preferably comprises a shield of selected thickness and/or material suspended in the window at the point closest the treatment site that attenuates or blocks a portion of the radiation from escaping the probe.

[00040] A first embodiment of a system 20 for precise positioning of the probe 18 is shown in Fig. 7. The positioning system 20 comprises a base 80 and contact extension 82 which serve as a reference member and are adapted to be mounted to the extra-ocular portion of the sheath or probe 18. Using the sclera (the surface of the eye) as a dimensional reference point or surface, a spring 84 is located on the probe 18 to provide a positive engagement of the contact extension 80 (when carried on the base 82) against the sclera during initial placement. See Figs. 8 and 9.

[00041] For purposes of assembly onto the probe, the base 80 has a slot 86 sized to fit over the probe 18 so that it can be placed thereon. The contact extension 82 also has a slot 88 thereon to facilitate placement on the probe 18 distally of the base 80. The contact extension 82 designed to seat on the base 80 and is maintained in position thereon by frictional engagement. A handle 90 is provided that has a threaded end 92 that is received in a complementarily-threaded aperture 94 in the base 80. The threaded end 92 of the handle 90 serves as a set screw to secure the base 80 in position on the probe 18 after initial placement, as will be discussed in greater detail below. The positioning system 78 may be made of any suitable material, but is preferably made of acetal.

[00042] With reference to Fig. 8, the probe is initially

positioned, with the tip 74 of the probe in light contact with the target area to be irradiated, touching either the retina or the CNV tissue under the retina. The spring 84 pushes the contact extension 82 mounted on the base 80 into contact with the sclera. The handle 90 is then turned to engage against the probe 18, thus locking the base 80 into position on the probe 18. The probe 18 is then withdrawn from the eye. With the base 80 locked in position on the probe, a spacer 96, which also has a slot 98 that permits it to be placed on the probe 18, is then placed between the base 80 and the contact extension 82, as seen in Fig. 9, to accurately set the distance between the treatment area and the probe tip 74.

[00043] In practice, the spacer 96 has a thickness of from about 0.5 to 3 mm, and preferably 1-1.5 mm (more preferably 1 mm), so as to create a space of the same distance between the tip 74 of the probe 18 and the target area. The particular spacing may vary with the eye disorder treated, the radiation source being used, and the size of the treatment area. A spacing of 1-2 mm (and preferably 1.5 mm) is the anticipated spacing for treating the neovascularized tissue associated with macular degeneration with a beta radiation source as described earlier. During the radiation delivery, the contact extension rests against the sclera, resisting or preventing further axial movement of the delivery device into the eye.

[00044] Alternatively, positioning of the probe tip can be facilitated by the use of intra-ocular ultrasound or doppler measurement of the distances between the distal end of the cannula and the target tissue. In such cases, the distal end of the cannula may include an ultrasound or doppler transducer (communicating with a read-out device) to both transmit and receive ultrasound or doppler waves. The data generated thereby is analyzed in real time, and a calculated measurement of the distance is presented on an optical readout or indicator. In a similar manner, optical interferometry devices and techniques can be employed for measuring the distance between the cannula tip and the target tissue.

[00045] Structures for assuring the proper spacing of the probe tip from the target site can take other forms. For example, as shown in Fig. 12, the tip of the probe 18 may include one or more balloons 100 that are inflatable upon locating the probe tip under the retina (R) in the bleb to insure for spacing of the probe tip between the retina and treatment zone. In addition, or alternatively, the distal end 101 of the probe 18 can be at an angle with respect to the axis of the probe where the radioactive source is located when in the treatment position (again shown in Fig. 12 - see also Fig. 15 and 17). The angled distal end 101 insures that a pre-determined minimum distance is maintained between the radioactive source and the target tissue.

[00046] In a second alternative, shown in Fig. 13, a preformed wire, or series of wires 102, are extendable from a lumen 104 in the probe to properly space or bump-off the probe tip from the treatment zone when advanced out of the lumen. A further alternative, shown in Fig. 14, is to use a retractable wire basket 106 that is advanced through a lumen 104 in the probe when the probe is placed at the treatment site. A still further alternative is to secure a optic fiber to the probe that extends beyond the distal end an amount corresponding to the desired spacing. When the optic fiber contacts the target tissue, the fiber darkens, thus alerting the surgeon to the desired spacing.

[00047] The basic procedure for sub-retinal intraocular brachytherapy according to the present invention is accomplished through standard vitrectomy and retinal detachment techniques, with the basic steps as follows. Prior to treatment, the surgeon confirms the location of the target tissue using retinal vascular landmarks and identifies the preferred location of the sclerotomy entry point (i.e., temporal, nasal, etc.) in order to limit exposure of the fovea during treatment. The surgeon will also want to confirm that the radiation source is properly positioned in the probe, when advanced to the treatment position. A device for testing for the proper positioning of the radiation source, and the method of its use, is disclosed in

the co-pending PCT application, "Test Device for Testing Positioning of a Radioactive Source and Method of Using Same," PCT/EP2004/012416, filed November 3, 2004, which is herein incorporated by reference.

[00048] Then the subject is prepared pursuant to standard vitrectomy procedures. Specifically, the pupil of the subject is dilated and the patient is positioned ventrally on the operating table. After appropriate cardiac and respiratory monitoring is established, and appropriate anesthesia is induced, the eye is anesthetized, such as with a retrobulbar or peribulbar anesthesia.

[00049] Next, the treatment area is accessed. A speculum is placed to secure the eye lid, and surgery begins with a conjunctival incision into the superotemporal, superonasal and inferotemporal quadrants of the eye to be treated. A scleral incision is made approximately 3 to 4 mm away from the surgical limbus in the inferotemporal quadrant, and an infusion cannula is inserted into the vitreous cavity. After confirming that the infusion cannula is positioned properly, the infusion line is opened and a second and third sclerotomy are created 3 to 4 mm away from the surgical limbus in locations determined prior to commencement of the surgery in the superonasal quadrant. An appropriate lens for vitreoretinal surgery is positioned and a vitrectomy performed, a standard endoilluminator being used to illuminate the vitreous cavity.

[00050] Next, the treatment probe is positioned. To this end, the spring 84 of the positioning system 20 is carefully slid over the probe 18 up to the device handle 16, and the positioning system is placed on to the probe shaft without the spacer element 96. See Fig. 8. The sclerotomy is extended to a length of approximately 1.3 mm, and the delivery probe is inserted through the sclerotomy incision into the vitreous cavity.

[00051] Under microscopic visualization, the surgeon places the tip of the probe directly above the macula. Specifically, the probe is positioned by gently touching the retinal tissue,

while directly holding the probe center marker (a mark on the probe tip designating the center of the radiation source) above the center of the CNV complex. While the surgeon holds the probe steady at this position, the positioning system (base 80 and contact extension 82) without the spacer 96 is secured onto the external portion of the delivery probe while in contact with the sclera to identify the precise location of the probe as it contacts the retina by tightening the handle, and the cannula is removed from the vitreous cavity. The spacer 96 is then placed between the positioning system base 80 and the contact extension 82, as shown in Fig. 9.

[00052] A localized retinal detachment (the "bleb") is created by using a sub-retinal infusion needle in the macular region, the bleb including the area of choroidal neovascularization. A new retinotomy is created on the temporal edge of the bleb, with the new incision created less than 4 mm away from the fovea to reduce the risk of a peripheral retinal tear. The retinotomy is approximately 1.3 mm in diameter in order to accommodate the probe. The delivery device probe 18 is then reinserted into the vitreous cavity and into the sub-retinal space through the second retinotomy, as seen in Fig. 10. The distal end of the probe is positioned directly above the center of the CNV complex with the positioning system touching the sclera, thus insuring the distance of the probe tip is about 1.5 mm above the target area.

[00053] Next, the radiation dose is delivered to the target tissue. To this end, the radiation source is advanced by pushing the slider mechanism towards the tip of the probe. Once advanced, the source wire is locked into position by locating the pin in the detent 62. After the appropriate treatment time, the slider mechanism is retracted to bring the radioactive source back to the storage and locked position. After insuring that the radioactive source has been fully retracted into its storage position, the delivery probe is removed from the bleb and withdrawn from the eye.

[00054] After removal of the probe, the retina is then

reattached intraoperatively, and a complete fluid-air exchange is performed, resulting in an air or gas tamponade in the vitreous cavity. The retinotomy is closed by, e.g., laser photocoagulation, if necessary, while the superior sclerotomy is closed with ophthalmic suture. The inferotemporal sclerotomy is closed, and the conjunctiva is sutured with appropriate ophthalmic sutures. A mixture of antibiotics and steroids may then be administered in the sub-conjunctival space.

[00055] In an alternate method, the retina and other non-target tissue during treatment may be shielded and protected by introducing a radiation-attenuating fluid into the bleb that is created by lifting the retina away from the CNV. The fluid can consist of saline, or a fluid with higher attenuation coefficient, such as contrast media. The use of a radiation-attenuating fluid to protect non-target tissue may also be advantageous during epi-retinal and epi-scleral applications of radiation. In such cases, the radiation-attenuating fluid is merely introduced into the interior of the eye, rather than into the sub-retinal space.

[00056] Maintaining the bleb shape during the course of the procedure is also important to minimizing the potential for damage to the photoreceptors. It is contemplated that the bleb shape may be maintained in several different ways. For example, the bleb shape may be maintained by injecting a high viscosity material into the sub-retinal space created by the bleb. Because of the material's high viscosity, its ability to flow through the retinotomy is reduced. The high viscosity material is removed, after treatment, using a standard vitrectomy device. One suitable high density material is a sodium hyaluronate preparation for ophthalmic use sold by Pharmacia Company, under the trademark HEALON®. A substance with variable viscosity having a high initial viscosity during the treatment time, with a lower viscosity thereafter, would further facilitate the removal of the material from the sub-retinal space upon completion of the procedure. A gelatinous substance whose viscosity can be reduced through the administration of a

diluting agent (e.g., water), a chemical agent (for adjusting ph), a temperature-charging agent or energy, photo reaction due to light administration, etc., would be suitable.

[00057] Other methods for maintaining the bleb shape include applying a sealing substance (such as HEALON®) to the retinotomy and the probe/cannula inserted therethrough to prevent the bleb from deflating by blocking the escape of fluid between the probe and the retinotomy. An inflation agent, such as saline, can also be continuously introduced into the sub-retinal space with a small positive pressure by means of an open lumen 108 associated with the cannula 18 (Figs. 15, 16). Further, the distal end of the cannula can be provided with a balloon (Fig. 12) that is inflated after the distal end of the cannula is introduced into the bleb in order to support the bleb and prevent the bleb from deflating or collapsing.

[00058] The potential for damage to the photoreceptors by the probe may also be minimized if the cannula has a low-friction surface. This can be provided by coating the probe with a lubricant or other coating, such as Teflon or electrolytic carbon, or providing the cannula with a highly-polished surface, as by electro-polishing. Alternatively, the backside 110 of the probe (i.e., the non-treatment side) can be relieved, as shown in Fig. 17, to lessen the degree of contact of the probe with the photoreceptors.

[00059] The prevention or limiting of bleeding from the retina into the sub-retinal space, and the removal of any residual blood that should form therein, is also important for protecting the photoreceptors. In this regard, the area of the incision resulting from the vitrectomy performed to create the bleb may be cauterized to prevent or limit retinal bleeding. Such cauterization may be achieved by diathermy, cryopexy, or the application of laser or RF energy using instrumentation and methods known for re-attaching the retina to the retinal pigment epithelium in the case of retinal detachment.

[00060] Additionally, or alternatively, blood coagulants, such as antihemophilic Factor VIII (recombinant) (available from

Bayer Healthcare as Kogenate), aminocaproic acid (available from Immunex as Amicar), and desmopressin acetate (available from Rhone Poulanc Rorer as Octostim), may also be injected into the sub-retinal space to limit bleeding by means of the separate lumen associated with the treatment device, as shown in Figs. 15, 16. The coagulant may also be removed through the same lumen. Injection of an iron-binding substance (such as apotransferrin) into the blood may also be used in facilitating the removal of blood from the sub-retinal space and preventing its oxidation.

[00061] After the CNV has been irradiated, an anti-proliferating drug (anti-Vascular Endothelial Growth Factor or anti-VEGF agent, such as pegaptanib sodium) may be injected into the sub-retinal space to prevent and/or limit further growth of the CNV.

[00062] It has been observed that hypoxic cells seem to recover better from radiation than healthy cells. Thus, it is believed that it would be beneficial to reduce the retinal blood supply of the non-target tissue during radiation treatment in order to facilitate the recovery of such tissue after being subjected to radiation. To this end, it is proposed that the tip of the probe include an inflatable balloon that causes pressure on the retina when inflated to reduce the blood flow thereto, the radiation treatment being performed through the balloon. Alternatively, it is proposed to protect the non-target tissue with a deployable mask made of a radiation-blocking material that will be deployed and located over the non-target tissue, while leaving the target tissue exposed. Such a material could be carried by the tip of probe 18 or by a separate device and deployed after formation of the bleb. The material could be biodegradable if desired.

[00063] The sub-retinal approach as described above, while believed to be effective in treating AMD, requires an extremely high degree of skill on the part of the ophthalmic surgeon to create the bleb and locate the treatment cannula in the sub-retinal region. Accordingly, the delivery device of the present

invention may also be used in methods for intraocular, epi-retinal application of radiation, in which no bleb is created.

[00064] Performance of the epi-retinal method is substantially easier than the sub-retinal approach. Intraocular access made simply through a sclerotomy, and the distal end of the probe is located over the macula. No detachment of the retina or the creation of a bleb is required. Accurate placement of the probe may be accomplished by any of the positioning systems described. Ultrasound or Doppler techniques known in the art may also be used. Other mechanical methods may also be used, such as putting a stand-off fiber or "whisker" on the tip of the probe that touches the retina when the probe is properly positioned. Alternatively, an inflatable balloon that, when inflated, spaces the probe the desired distance from the target tissue can also be used.

[00065] In a further alternative, a miniature radiation sensor that can be remotely interrogated may be placed on the retinal surface, and the distance between the probe tip and the surface of the retina can be determined based upon the level of radiation measured by the sensor. If multiple (i.e. 3) sensors are used, triangulation of the measured radiation intensity would provide an accurate measurement of position. If at least three miniature event counters or sensors are positioned in an array on the periphery of the retina equidistant from the target tissue, the intensity/frequency of events measured by each point can be analyzed and then compared. The position of source then can be determined through well-known three-dimensional triangulation calculations at the beginning of the radiation administration. The event counters/sensors can be placed either in the eye; behind the eye, or even on the front surface of the eye, if the radiation source produced a sufficient emission to be measured externally. Alternatively, the radiation source can carry a small transducer on its tip that would emit a "ping" that can be picked up by receivers positioned as described above. Other signaling/receiving systems such as light or RF can also be used. As a further method, a permanent magnet

disposed on the tip of the device could produce a sufficient Galvanic effect in appropriate sensors to be measurable, especially in an epi-retinal application where the size constraints of the device are less critical. A digitally-enclosed signal would provide improved speed and accuracy.

[00066] It will be understood that the embodiments and methods of the present invention that have been described are illustrative of the application of the principles of the present invention. Numerous modifications may be made by those skilled in the art without departing from the true spirit and scope of the invention, including combinations of the features that are individually disclosed or claimed herein.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A device for local, directional delivery of radiation to intraocular target tissue comprising:

a radiation source;

a cannula sized for intraocular insertion into an eye and having a proximal end and a distal end for receiving the radiation source, the cannula being fluid tight so as to prevent contact of body fluids with the radiation source; and

a housing to which the proximal end of the cannula is secured for moving the radiation source between a retracted proximal position and a treatment position at the distal end of the cannula, the housing comprising an advancement mechanism operatively coupled to the radiation source, the advancement mechanism being movable to move the radiation source between the retracted position and the treatment position,

wherein the radiation source is a radioactive source wire having a distal end and a proximal end for local delivery of radiation to a target tissue comprising:

a relatively stiff proximal portion;

a relatively flexible distal portion joined to the proximal portion;

and

a radioactive source secured to the distal end of the source wire, wherein the proximal and distal portions comprise steel braided wire with a connection therebetween and a sleeve for reinforcing the connection of the proximal portion to the distal portion.

2. The radiation delivery device of claim 1 wherein the housing comprises a shielding zone for shielding the radiation source in the retracted position.

3. The radiation delivery device of claim 1 wherein the housing provides a positive visual indication of the retracted and treatment positions of the radiation source.
4. The radiation delivery device of claim 1 wherein the advancement mechanism is lockable in the retracted position.
5. The radiation delivery device of claim 1 wherein the housing includes an elongated slot having first and second ends through a surface thereof and the advancement mechanism can be manipulated through the slot so that the radiation source can be moved between the retracted and treatment positions.
6. The radiation delivery device of claim 1 wherein the distal end of the radiation source is sufficiently flexible to allow unimpeded mechanical transport through the cannula around a radius of curvature of from 4 to 8 mm.
7. The radiation delivery device of claim 1 wherein the radiation source is radioactive and the device further comprises a source delivery wire attached to the radioactive source, wherein the source delivery wire has proximal and distal ends and wherein the proximal end and the distal end of the radioactive source wire comprise steel braided wire with a connection therebetween, and a sleeve for reinforcing the connection of the proximal end to the distal end.
8. The radiation delivery device of claim 1 wherein the radioactive source emits beta radiation.
9. The radiation delivery device of claim 1 further comprising a separate lumen associated with the cannula having an opening adjacent the distal end of the cannula, a wire having a distal end that is slidably received in the lumen,

and an expandable structure at the distal end of the wire, the structure expanding as the distal end of wire exits the opening of the lumen.

10. The radiation delivery device of claim 1 wherein the cannula further comprises at least one inflatable balloon located at the distal end thereof, and a separate lumen for selectively inflating and deflating the balloon.

11. The radiation delivery device of claim 1 wherein the cannula further comprises a separate lumen having an opening at the distal end of the cannula through which fluid may be selectively administered or withdrawn.

12. The radiation delivery device of claim 1 and further including a radiation window at the distal end of the cannula for providing a desired radiation dose profile when the radiation source is received therein.

13. The radiation delivery device of claim 12 wherein the cannula comprises a tubular member with at least one lumen that is connected to the housing, the distal end thereof including a cover covering the window with a fluid-tight seal.

14. The radiation delivery device of claim 13 wherein the tip of the window comprises platinum-iridium material.

15. The radiation delivery device of claim 1 wherein the distal portion is sufficiently flexible to allow unimpeded mechanical transport through a cannula around a radius of curvature of from 4 to 8 mm.

16. The device of claim 1 wherein the radiation source is a radioactive source wire having a proximal end and distal end comprising: a leading strand at the distal end having sufficient flexibility so as to allow unimpeded

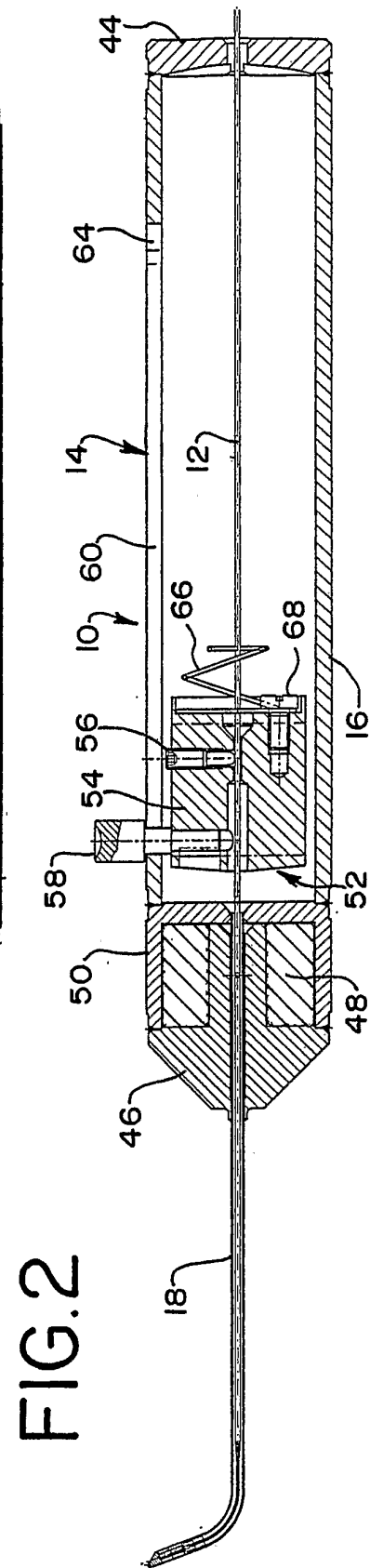
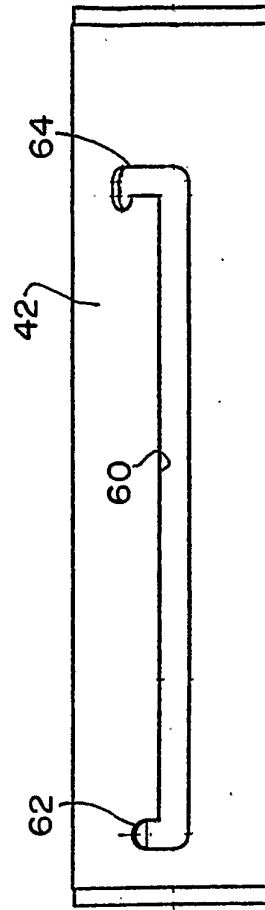
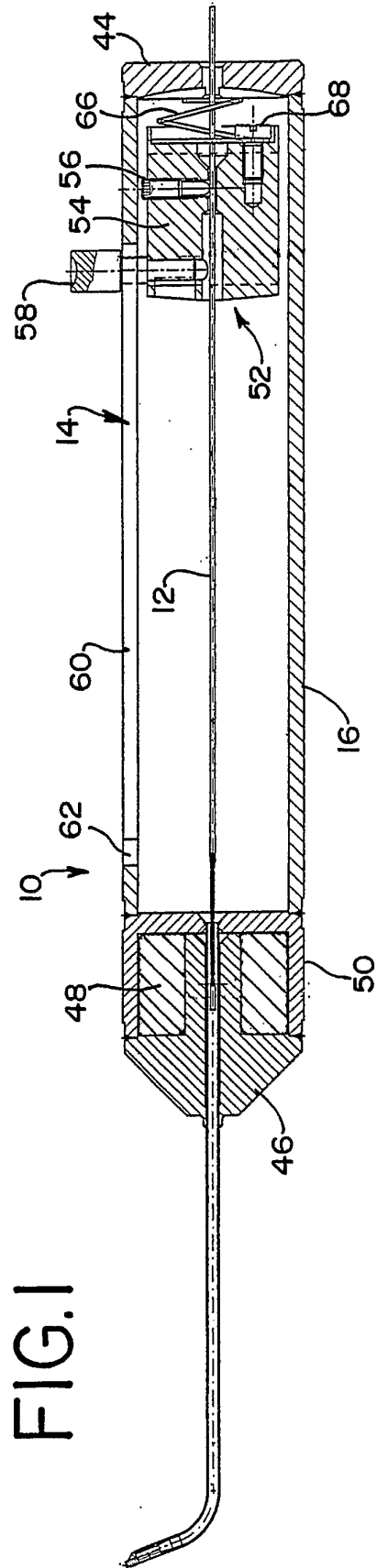
mechanical transport through a cannula around a radius of curvature of from 4 to 8 mm; a handle strand at the proximal end having greater stiffness than the leading strand; a tubular sleeve for securing the leading strand to the handle strand and secured to the leading strand and handle strand by welding; a radioactive source comprising a canister holding a radioactive seed secured to the distal end of the leading strand; a reinforcing sleeve at the junction of the canister and the leading strand for securing the canister to the leading strand; and a reinforcing tubing at the proximal end of the handle strand.

Dated this 7th day of February 2011.

Neo Vista, Inc.

Patent Attorneys for the Applicant

PETER MAXWELL AND ASSOCIATES



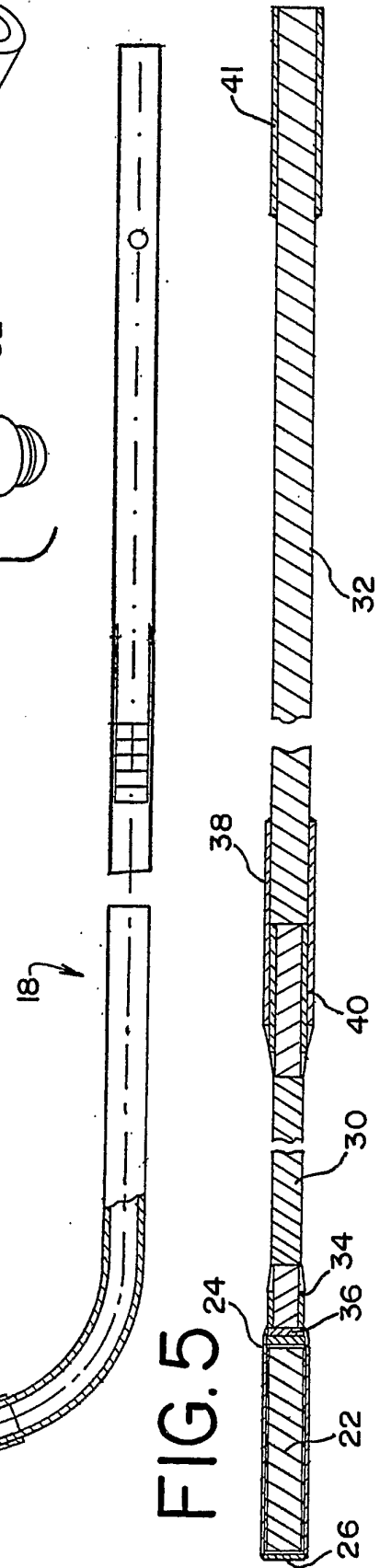
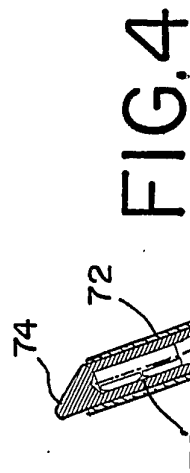
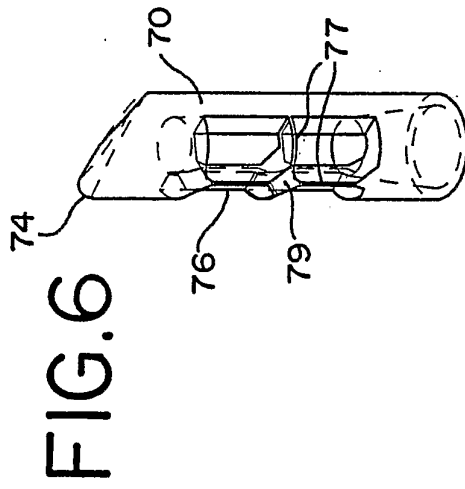
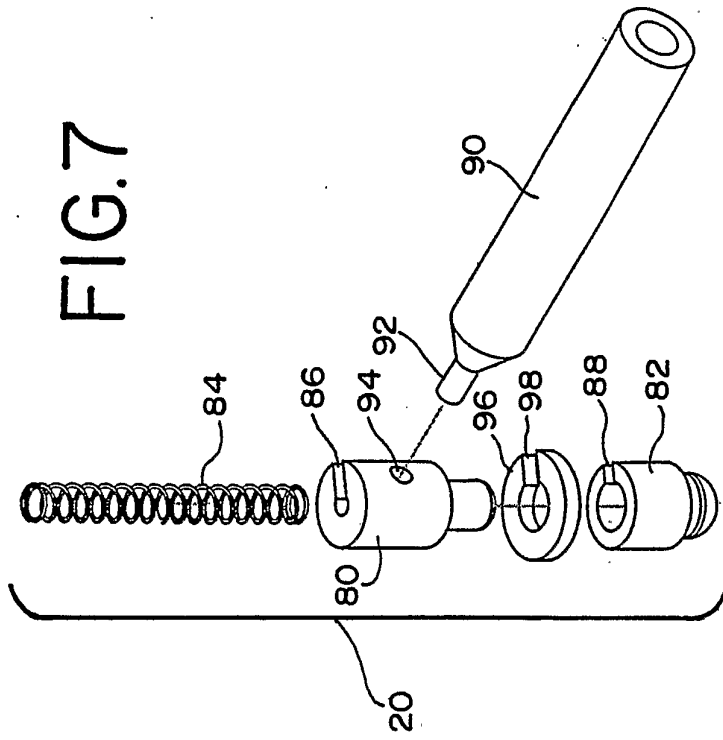


FIG.8

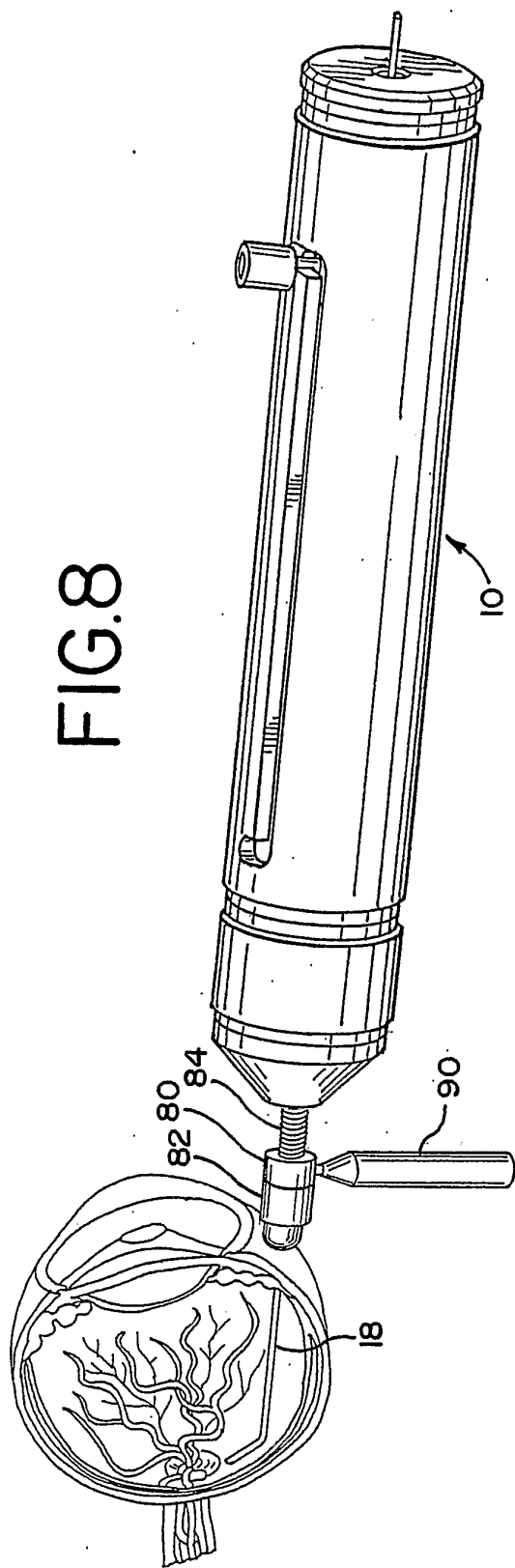


FIG.9

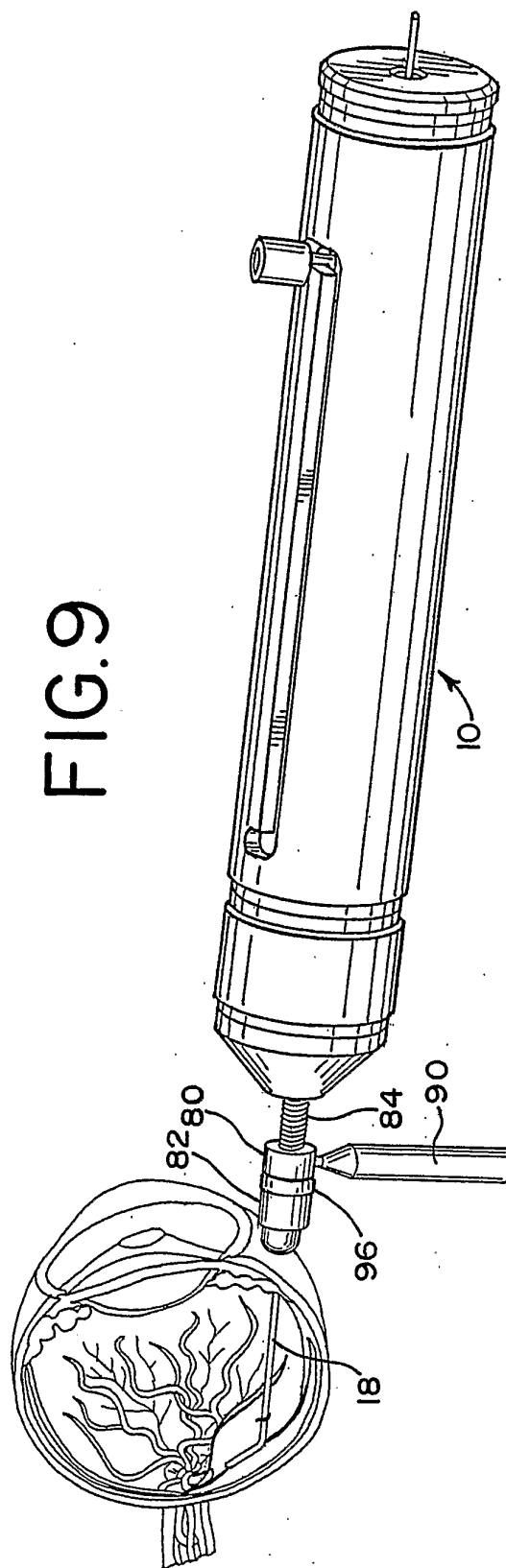


FIG. 10

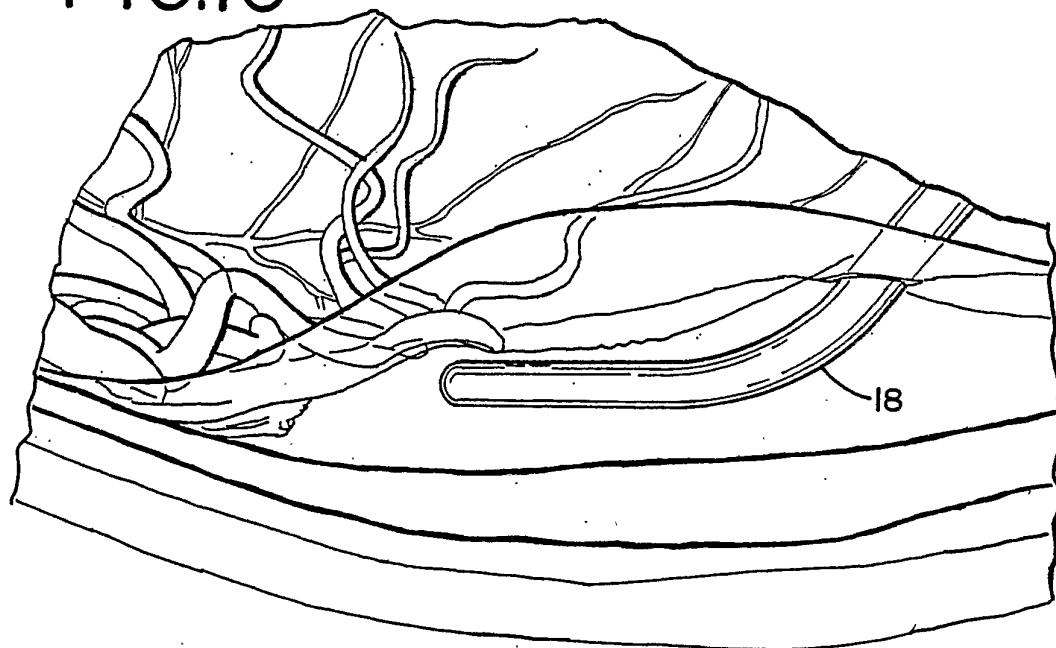


FIG. 11

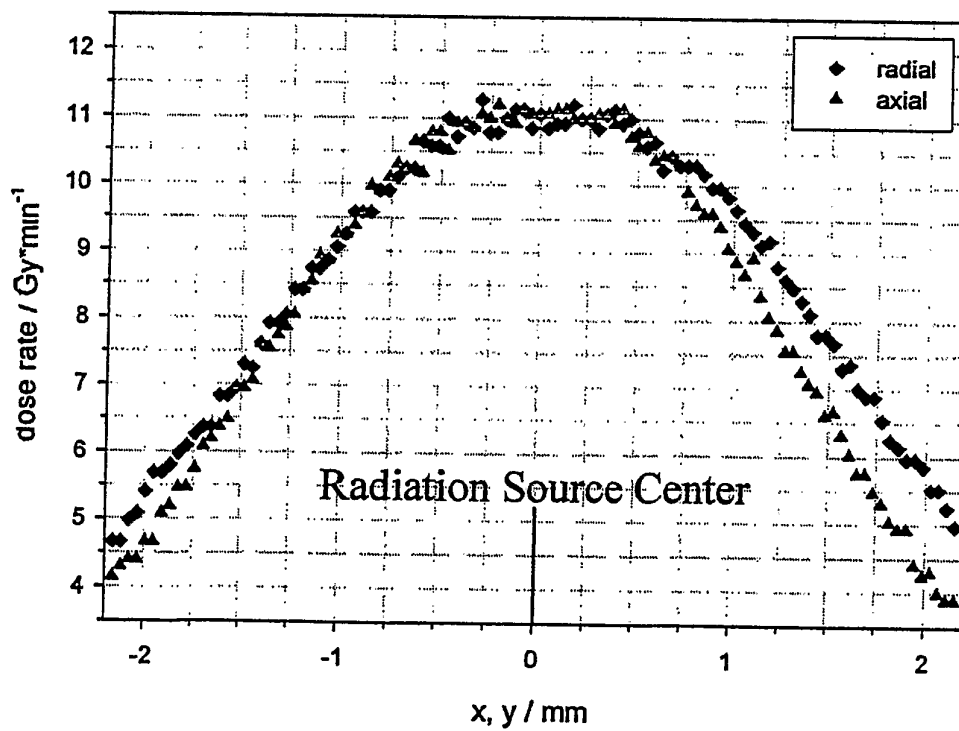


FIG. 12

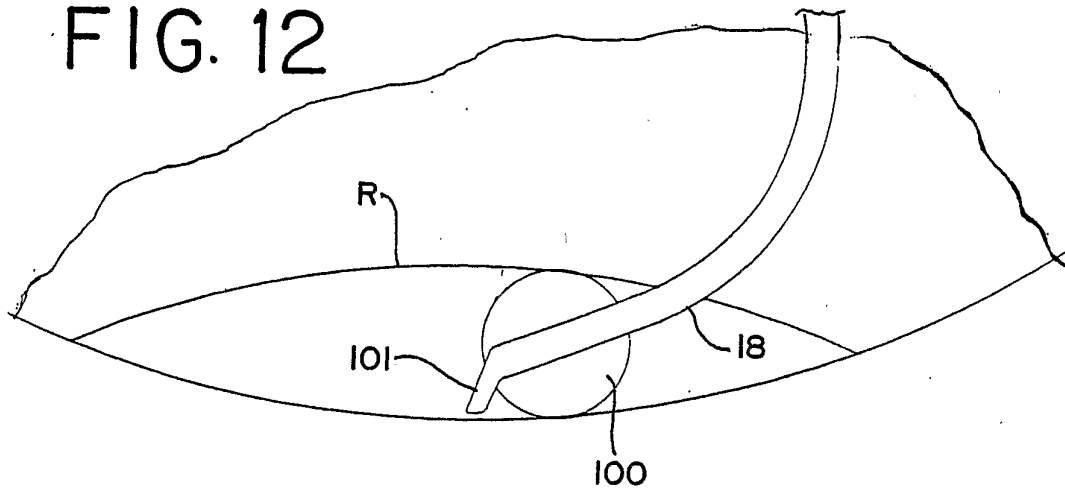


FIG. 13

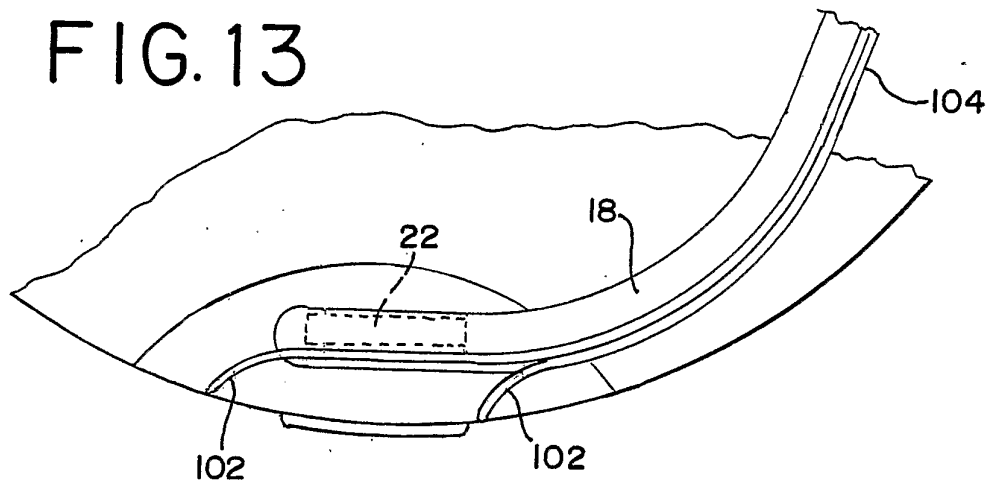


FIG. 14

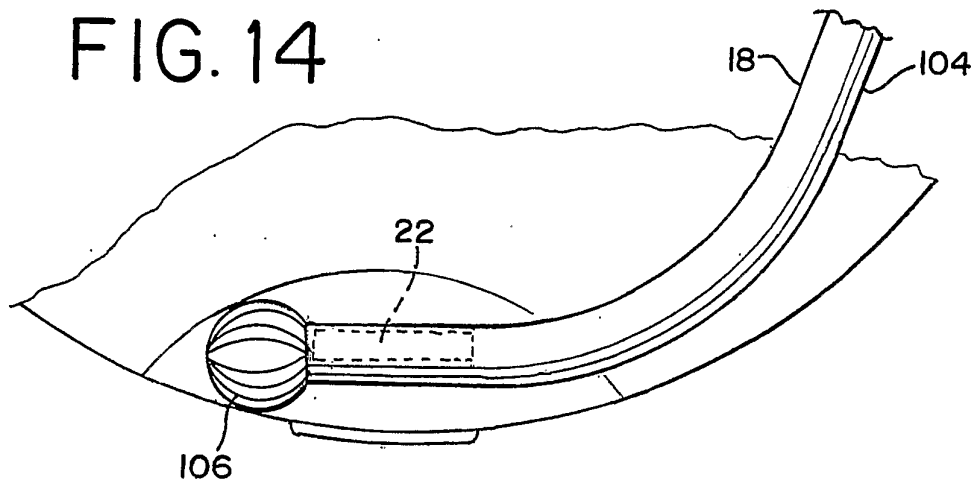


FIG. 15

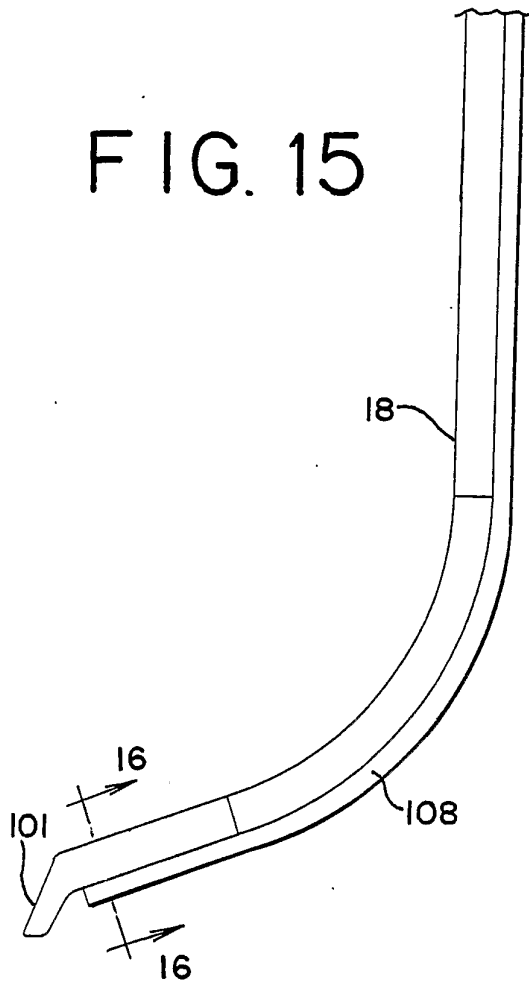


FIG. 16

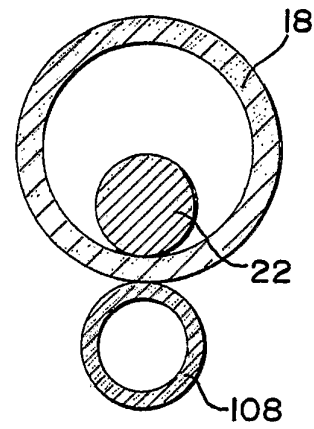


FIG. 17

