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An agency of Industry Canada

CA 2539191 A1 2005/05/06

(21) 2 539 191

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2004/09/15
(87) Date publication PCT/PCT Publication Date: 2005/05/06
(85) Entrée phase nationale/National Entry: 2006/03/15
(86) N° demande PCT/PCT Application No.: US 2004/030235
(87) N° publication PCT/PCT Publication No.: 2005/039384
(30) Priorités/Priorities: 2003/09/15 (US60/503,134);
2004/09/14 (US10/940,131)

(51) Cl.Int./Int.Cl. *A61B 17/00* (2006.01),
A61B 17/94 (2006.01)

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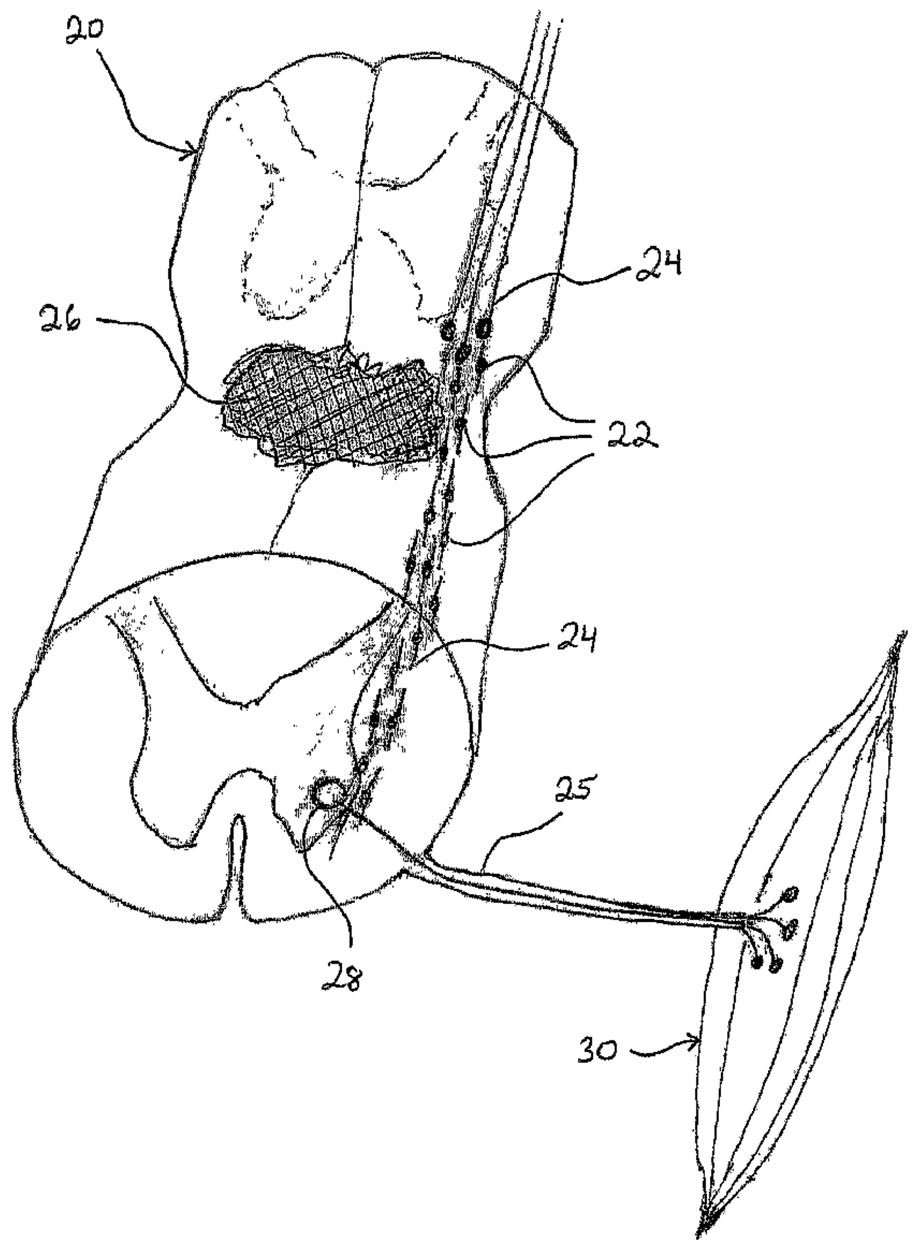
(54) Titre : PROCEDE ET SYSTEME DE TRANSPLANTATION CELLULAIRE
(54) Title: METHOD AND SYSTEM FOR CELLULAR TRANSPLANTATION



(57) Abrégé/Abstract:
The present invention provides a method for treating an injury of a spinal cord of a patient. The method includes implanting a therapeutic substance in the spinal cord under indirect visualization. The indirect visualization may be provided by an endoscope, and the therapeutic substance may include cells. The present invention also provides a device for treating an injury of the spinal cord. The device includes skin visualization means for visualizing the spinal cord through a skin puncture, and injection means for injecting a therapeutic substance into the spinal cord.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 May 2005 (06.05.2005)

PCT

(10) International Publication Number
WO 2005/039384 A2

(51) International Patent Classification[7]: A61B

(21) International Application Number:
PCT/US2004/030235

(22) International Filing Date:
15 September 2004 (15.09.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/503,134	15 September 2003 (15.09.2003)	US
10/940,131	14 September 2004 (14.09.2004)	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,

[Continued on next page]

(54) Title: METHOD AND SYSTEM FOR CELLULAR TRANSPLANTATION

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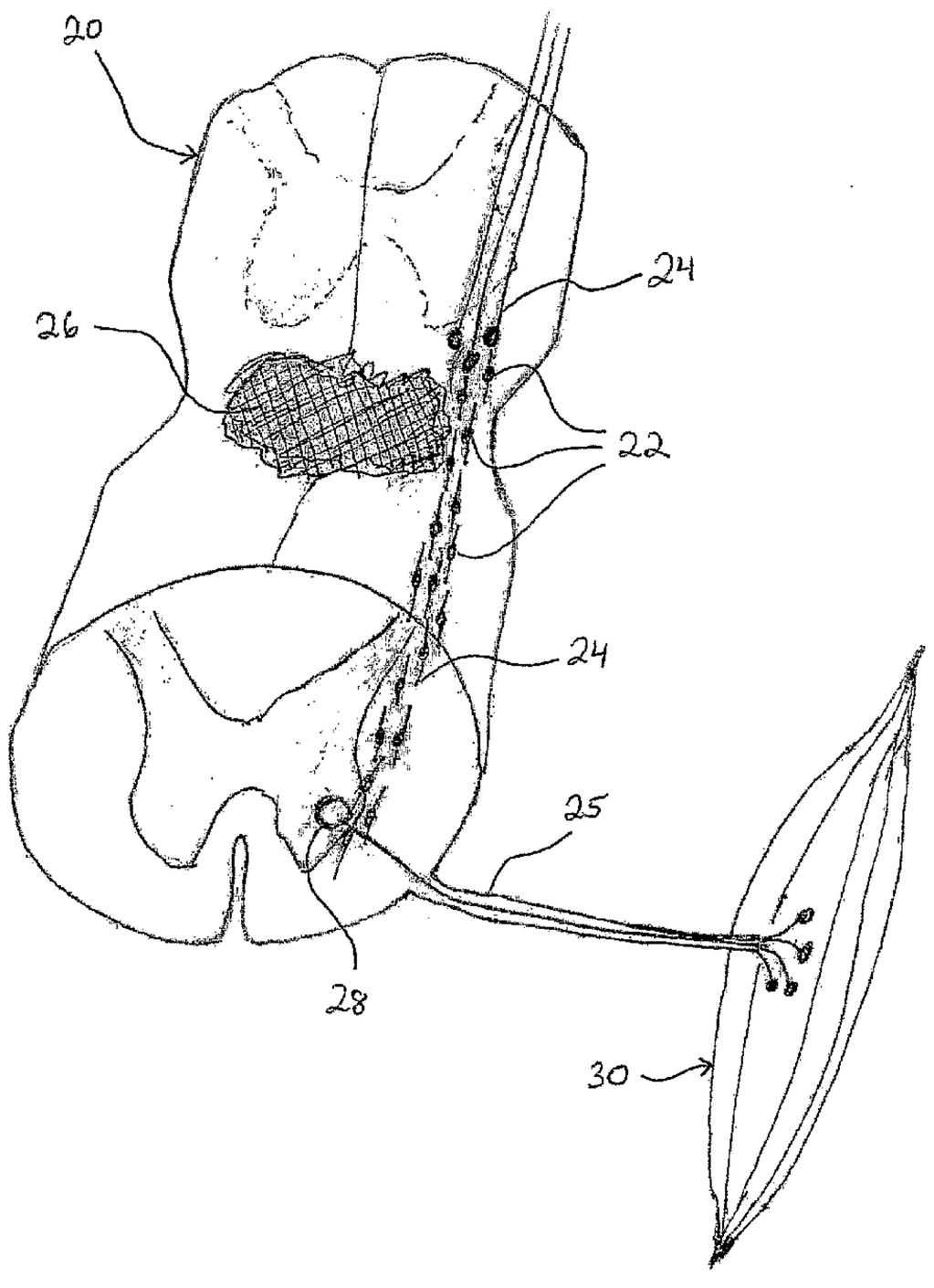


WO 2005/039384 A2

WO 2005/039384 A2

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, IT, 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.

METHOD AND SYSTEM FOR CELLULAR TRANSPLANTATION

FIELD OF THE INVENTION

The invention relates generally to a method and system for cellular transplantation, and in particular, to percutaneous endoscopic cellular transplantation into the spinal cord to create intramedullary cellular trails.

BACKGROUND OF THE INVENTION

Stereotaxic injection into the brain is facilitated by secure cranial immobilization in a stereotaxic frame. This has made it possible to accurately place transplants in the brain. However, stereotaxic injection into the spinal cord is more difficult due to the small size of the spinal cord, its constant motion in several planes relative to the vertebral spine, and its exquisite vulnerability to injury. For these reasons current spinal cord injection techniques rely upon direct visualization of the spinal cord during an open surgical procedure and immobilization of the spine in clamps during cellular injections. Since this type of surgical exposure is usually necessary to create an experimental spinal cord injury, various types of transplant techniques are possible using the same exposure.

Many spinal injuries require decompression and vertebral column stabilization surgery soon after hospitalization. This surgical opportunity may not be an optimal time for cellular injection to facilitate repair. Once this initial surgery has occurred, it is undesirable to disturb the progress of wound healing and bone fusion. Therefore, it is important to develop strategies of cell transplantation into the spinal cord compatible with minimal disturbance of the wound healing process. Cellular transplantation into the injured spinal cord has been used to study injury and repair responses in experimental models. Some clinical trials of cellular transplantation (e.g. activated macrophages, ensheathing glia) into the injured human spinal cord have been initiated using conventional open surgical techniques. Cell suspensions can be transplanted to create trails or columns of cells to partially reconstruct axonal pathways. In the spinal cord this requires either several closely spaced separate injections or a technique to enter the cord at a shallow angle. Currently, almost all injections into the spinal cord result in a tract defined by the needle path which is generally perpendicular to the longitudinal axis of the spinal cord.

There exists a need for a minimally invasive technique and system for cellular delivery in the spinal cord. Accordingly, the present invention provides a minimal access endoscope-assisted technique via a lumbar puncture approach without the need to create a large surgical incision. Cellular transplantation is performed under endoscopic visualization based on percutaneous access, remote from the injury site. Delivery of cells or cell suspension provides a trail of cells in the spinal cord which may span from the site of axonal injury to a useful target neuronal population. Regeneration of the damaged axons to the target neuron occurs via the transplanted supportive cells. The trail of cells is defined by the needle path which is generally parallel to the longitudinal axis of the spinal cord.

SUMMARY OF THE INVENTION

Spinal cord injections may be performed by introducing an endoscope percutaneously at an interlaminar space, for example a lumbosacral interspace. Because the epidural and subarachnoid spaces can be distended with fluid injection, endoscopic visualization of structures in these spaces can be achieved. The endoscope may be used with a syringe to inject a cellular suspension using a small catheter and endoscopically directed needle placed through the working channel of the endoscope. The system and method results in a columnar trail of transplant cells.

This strategy for intraspinal injection may confer important clinical advantages over other techniques. For example, using an endoscopic procedure instead of a CT-guided percutaneous technique, the spinal cord surface blood vessels can be visualized and avoided to prevent bleeding. Also, orientation to the midline is improved, and the depth of the needle insertion can be directly determined. As a further advantage, insertion of the endoscope at a non-injured site permits a cautious traversal of the endoscope from a normal region into the injury region of the spinal cord, thereby improving visual orientation. Also, the present invention eliminates the need for a laminectomy to access the spinal cord, facilitates flexibility of timing between surgical decompression and transplantation operations, reduces interference with healing of previous surgical incisions and fusion beds, facilitates multiple episodes of transplantation at different sites, reduces surgical duration, and may be performed under local anesthesia.

In accordance with one aspect of the present invention, there is provided a method for treating an injury of a spinal cord of a patient. The method includes implanting a therapeutic substance in the spinal cord under indirect visualization, such as an

endoscope. The endoscope may be inserted through a skin puncture site remote from the injury of the spinal cord and through an interlaminar space of the patient, such as a lumbosacral interspace.

The method may further include inserting an injection member through the skin puncture site and into the spinal cord and injecting the therapeutic substance through an aperture of the injection member. The injection member may be at least partially withdrawn from the spinal cord while injecting the therapeutic substance to thereby form a trail of therapeutic substance. The injection member may be slideably disposed in a working channel of the endoscope and may include a needle connected to a catheter. The distal portion of the needle may be inserted into the spinal cord.

The method may also include reducing or damping motion of the needle in the spinal cord relative to the endoscope by providing a flexible portion of the catheter between the needle and a distal end of the endoscope. The therapeutic substance injected into the spinal cord may be cells, a cell suspension, or a biological matrix containing a therapeutic substance(s). The method may further include injecting distention fluid in the interlaminar space.

In an exemplary embodiment, the method may include the insertion of an implant into the patient. Use of percutaneous endoscopy may place syringopleural or cystoperitoneal cerebrospinal fluid (CSF) shunts within the spinal cord. Endoscopically-assisted shunting of intramedullary syringes, an arachnoid cyst, and/or a perineurial cyst may be performed.

In accordance with a similar aspect of the present invention, the injection member may include a catheter connected to a needle with a side-hole aperture. A flexible hollow guide wire may be positioned through the catheter and side-hole aperture of the needle and into the spinal cord. The therapeutic substance may be injected from the hollow guide wire while the guide wire is being withdrawn from the spinal cord to thereby form a trail of therapeutic substance in the spinal cord.

In accordance with another aspect of the present invention, a device is provided for treating an injury of the spinal cord of a patient. The device includes a visualization means for visualizing the spinal cord through a skin puncture located remote from the injury and an injection means for injecting a therapeutic substance into the spinal cord. The visualization means may be provided by an endoscope. The injection means may be withdrawn while injecting the therapeutic substance to thereby form a trail of therapeutic substance in the spinal cord. The device may also include means for fluid distention of an

interlaminar space of the patient. Fluid distention facilitates endoscopic visualization because the optical density of the fluid permits illumination and visualization.

BRIEF DESCRIPTION OF THE DRAWINGS

A more complete understanding of the present invention, and the attendant advantages and features thereof, will be more readily understood by reference to the following detailed description when considered in conjunction with the accompanying drawings wherein:

Figure 1 illustrates a trail of cells implanted through a site of a spinal cord injury;

Figure 2 illustrates an exemplary system for endoscopic cellular transplantation;

Figure 3A is a photograph of exemplary endoscopes and related apparatus for use with the present invention;

Figure 3B is an expanded view of the distal ends of the endoscopes, catheters, and needles of Figure 3A;

Figure 4A shows a needle with a stylet positioned within the subarachnoid space of the patient;

Figure 4B shows an introducer placed over the needle;

Figure 4C shows an endoscope positioned in the introducer;

Figure 5A is an endoscopic view of the dorsal spinal cord;

Figures 5B and 5C are endoscopic views of nerve roots and blood vessels of the spinal cord;

Figure 5D is an endoscopic view showing a needle within the dorsal spinal cord;

Figure 6 is a fluorescent photomicrograph of a spinal cord section showing fluorescent fibroblasts after injection in the spinal cord;

Figure 7A shows a fluid filled cavity of an injured spinal cord being treated with transplanted cells;

Figure 7B shows a large quantity of cells occupying the cavity;

Figure 7C shows a collapse of the fluid cavity after injection and integration of the cells;

Figure 8 illustrates the distal end of the endoscope with the catheter and needle disposed in the working channel of the endoscope;

Figure 9 illustrates the distal end of the endoscope with a flexible portion of the catheter positioned between the needle and endoscope;

Figure 10 illustrates a catheter advance device for use with the present invention;

Figure 11 illustrates another exemplary embodiment for cellular transplantation;

Figure 12A illustrates an exemplary embodiment of the present invention with multiple percutaneous puncture sites; and

Figure 12B illustrates a trail of cells transplanted within the spinal cord.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method and apparatus for making a percutaneous cellular injection into the spinal cord under endoscope visualization. The method includes percutaneously introducing a flexible endoscope into the subarachnoid space of the spinal cord, introducing a flexible catheter with an attached needle into a working channel or lumen of the endoscope, penetrating the spinal cord with the needle under direct visualization of the endoscope, and injecting cells into the spinal cord while the needle is withdrawn. The steps of penetrating the spinal cord and injecting cells into the spinal cord result in the implantation of a trail of cells within the spinal cord.

The system of the present invention provides for minimally invasive transplantation of cells within the spinal cord. A visualization means provides percutaneous viewing of the spinal cord (and/or interlaminar space, lumbosacral interspace, arachnoid, subarachnoid, pia mater). An injection means provides for the injection of cells into the spinal cord. The injection means may be configured for insertion through a working channel of the visualization means. The system provides a trail of implanted cells within the spinal cord.

Referring now to Figure 1, a portion of a spinal cord 20 having a trail of cells 22 implanted therein is illustrated. The cellular trail 22 may connect severed axons, neurons, and/or axons and neurons thereby leading to spinal cord repair. Severed axons 24 of a descending tract sprout and elongate along the trail of transplanted cells 22. The trail of cells 22 crosses an injured site 26 of the spinal cord 20 providing a bridge for axonal growth. The trail of cells 22 may allow regrowth to a target neuron 28 that sends axons 25 to an effector organ 30, such as a muscle. The transplanted cells may be implanted in a linear or non-linear configuration. Preferably, the trail of cells follows a path of the shortest distance between two connection points. However, the trail of cells may also take a curved or winding path. For example, an injured region of the spinal cord may prevent a linear trail of cells from being transplanted, so the trail of cells may curve around the injured region.

Figure 2 illustrates an exemplary embodiment of the present invention. A cannula 32 is percutaneously positioned through the soft tissue near the spinal cord 20. The flexible distal portion 33 of an endoscope 34 is inserted through the cannula 32 so that the distal portion 33 of the endoscope 34 is in the interlaminar space, lumbosacral interspace, arachnoid, subarachnoid, and/or pia mater. The endoscope 34 is connected to a video camera 36, and an image of the spinal cord 20 can be seen on a monitor 38. An injection catheter 40 with a needle 42 enters the endoscope 34 through the working channel port 44. The distal portion of the needle 42 is placed into the spinal cord 20 at a specific location. The proximal portion of the injection catheter 40 is connected to a microsyringe 46. One mm marks or other indicia may be placed on the catheter 40 to enhance accuracy of catheter advancement.

Figures 3A and 3B illustrate two exemplary endoscopes for use in the present invention. It should be understood that any endoscope may be used with the present invention. Preferably, an endoscope with a working channel may be utilized. As seen in Figure 3A, a MYELOTEC endoscope 34a includes a catheter module 35. A microsyringe 46 and catheter 40 are inserted into the catheter module 35. A CODMAN endoscope 34b is also shown. A microsyringe 46 and catheter 40 are inserted into the CODMAN endoscope 34b. As seen in Figure 3A, the distal portion of the catheter module 35 is illustrated. The distal portion of the endoscope 34a is shown extended beyond the distal tip of the catheter module 35. The cell-filled catheter 40 and injection needle 42 are positioned in a working channel of the catheter module 35 and extend beyond the distal tip of the catheter module 35. The distal portion of the CODMAN endoscope 34b is shown with the cell-filled catheter 40 and injection needle 42 extended beyond the distal tip of the endoscope 34b. It is contemplated that other indirect visualization devices, such as MRI, CT scan, fluoroscopy, ultrasound, and X-ray, may be used with the present invention or used in combination with an endoscope.

Figures 4A-4C illustrate an exemplary method of the present invention. A needle 41 with a stylet 48 is inserted through the patient's skin and into the subarachnoid space 50 of the spinal column. A peel-away introducer 52 is positioned over the needle 42 and inserted into the subarachnoid space 50. An endoscope 34 with a projecting catheter 40 and needle 42 is inserted into the introducer 52, and the distal portion of the endoscope 34 is inserted into the subarachnoid space 50. A syringe 46 containing cells and/or other therapeutic agent(s) is placed in fluid communication with the catheter 40 and needle 42. Using endoscopic visualization, the needle 42 is advanced distally to perforate the pia

surrounding the spinal cord 20 and penetrate the spinal cord 20 to a desired depth. The syringe 46 is depressed pushing the cells and/or other therapeutic agent 22 into the spinal cord 20. If desired, while the cell suspension or other therapeutic agent is pushed from the syringe, the needle may be slowly withdrawn from the spinal cord to create a trail of cells. Furthermore, multiple rounds of transplantation could be performed at progressively distal sites to support regeneration over longer distances.

Another syringe 54 may be placed in fluid communication with the working channel of the endoscope 34. Distention fluid may be injected into the subarachnoid space 50 using the syringe 54.

In addition, the proximal end of the catheter may include indicia such as 1 mm marks to accurately determine how deep the needle has penetrated into the spinal cord. Also, a PE-10 polyethylene (or other suitable polymer) catheter may be used to hold the injection needle which may be a 30G cut-down needle tip extending approximately 5 mm from the end of the injection catheter and set about 3 mm into the catheter. The PE-10 catheter may have an inner diameter of about 0.28 mm and a length of approximately 58 cm. As such, a volume of 35.7 µl of cell suspension may be pre-loaded into the catheter. The catheter may be back-filled with a cell suspension so that a continuous fluid column exists in the catheter. The continuous fluid within the catheter and syringe system provides uniform injection pressure thereby facilitating uniform cell dispersion.

The endoscope may be rotated after positioned in the subarachnoid space to optimize the relative positions of the optical and illumination fiber bundle, the working channel, and the dorsal spinal cord to perform the injection. Distention of the subarachnoid space with isotonic fluid may be useful prior to the injection since the endoscopic visualization is enhanced in a fluid filled space. The distention may be delivered by attaching tubing in fluid communication with the working channel of the endoscope so that fluid can be injected via the working channel beside the injection catheter. The fluid infusion pressure may be approximately 30-35 cm H_2O and about 100 cc of fluid may be delivered during the procedure.

It is further contemplated that different injection parameters such as volume and injection rate may be utilized to minimize spilling the cell solution into the adjacent subarachnoid space. Also, distension fluid infusion may be stopped just before the cell injection is started to reduce the chance that the flow of fluid would cause cells to disperse from the injection site to other levels of the neuroaxis. Furthermore, the endoscope, catheter, and/or needle may be inserted through the patient's skin at a location

distant from the cellular injection site. As an example, for a L1 level injury of the spinal cord conus medullaris, the endoscope is introduced at L5/S1 and then directed several centimeters rostral to the level just distal to the cord injury where the injection could be made provided the subarachnoid space was open. This increases the safety of the procedure by allowing the operator to become oriented to normal anatomic structures prior to entering the subarachnoid space surrounding the areas of spinal cord injury.

Figures 5A-5D show images of the spinal cord as viewed from the endoscope. Figure 5A shows a dorsal portion of the spinal cord 20. Figures 5B and 5C show nerve roots 56 and blood vessels 58 of the spinal cord 20. Figure 5D illustrates the injection catheter with the needle 42 positioned within the dorsal spinal cord. In an exemplary embodiment, following pial perforation, the needle may be advanced by pushing the catheter into the endoscope working lumen. The cell suspension may be injected into the spinal cord, and the remainder may be injected while the needle is slowly withdrawn from the spinal cord over a period of time. Then, the needle may be left in position for another period of time before being withdrawn from the spinal cord parenchyma. Furthermore, by avoiding the extensive scarring associated with a laminectomy, the potential to perform multiple cell injections at progressively distal sites to support regeneration over a greater distance is facilitated.

Figure 6 illustrates a trail of fluorescent fibroblasts 22 after endoscopic injection. The trail of fibroblasts 22 extend from the distal dorsal surface 60 of the spinal cord 20 to the ventral surface 62 of the spinal cord 20. It is further contemplated that iron oxide or other suitable contrast agent may be combined with the transplantation cells, cell suspension, or therapeutic agent. Using magnetic resonance imaging, the iron oxide may be visualized to thereby verify accurate implantation of the trail of cells. MRI visualization of the iron oxide and cells may be used during injection of the cells into the spinal cord as well as after implantation of the cells to ensure proper placement. Also, orientation of the injection system to the midline of the spinal cord may be facilitated by injections of small pulses of radiopaque contrast material. This technique helps establish that the injection needle is localized within the target site of the spinal cord, such as within a syringomyelic cavity.

Representing another exemplary embodiment of the present invention, Figures 7A-C illustrate treatment of syringomyelia disease within the spinal cord. Figure 7A shows an introducer 52 positioned through the skin of a patient. An endoscope 34 is inserted through the introducer 52 with the flexible distal end 33 of the endoscope 34

placed into the subarachnoid space 50 of the spinal column. A syringe 46 containing cells and/or other therapeutic agent is placed in fluid communication with the catheter and needle 42. Using endoscopic visualization, the needle 42 is advanced distally to perforate the pia surrounding the spinal cord 20 and penetrate the spinal cord 20 to a desired depth within an expansile fluid-filled cavity 63 characteristic of syringomyelia. The syringe 46 is depressed pushing the cells 22 into the cavity 63 within the injured spinal cord 20. Figure 7B shows a large quantity of transplanted cells 22 occupying the volume of the cavity 63. Following glial integration of the transplanted cells 22, the cavity 63 collapses, and there is no longer a progressive expansile fluid cavity 63, as seen in Figure 7C.

Referring to Figures 8 and 9, the distal end of the endoscope 34 is illustrated. The endoscope 34 includes a lens or camera 64, an illumination bundle or rod 65, and a working channel or lumen 66. A catheter 40 is positioned within the working channel 66 of the endoscope 34. An injection needle 42 is inserted within the catheter 40. This configuration may provide the advantage that while the tubing 40 and needle 42 are partly within the endoscope working channel 66 they behave with similar rigidity to the endoscope 34, allowing controlled and accurate placement of the needle 42. As seen in Figure 9, the device may be designed to minimize injection-related spinal cord trauma due to spinal cord motion relative to the needle 42 by using a segment of flexible tubing 68 between the endoscope 34 and the injection needle 42 to allow the needle 42 to move with the spinal cord during physiologic motion. Additionally, to facilitate this motion damping feature, the endoscope may be retracted while the needle is left in position within the spinal cord.

Figure 10 illustrates a three-way locking stopcock device 70 that can be used to control advancement of the catheter 40. A flexible injection catheter 40 is passed through the three way stopcock 70. A spring-loaded serrated wheel, gear, knob, cam, lever, etc. 72 can be rotated to advance the catheter 40 with a needle. The wheel 72 may be retracted in order to allow the endoscope to move relative to the needle and catheter 40. Using a button 74, the serrated wheel 72 can be pulled away from the flexible catheter 40 permitting the endoscope to be moved with respect to the catheter 40 after the needle is placed into the spinal cord, and also during advance of the catheter 40 through the endoscope. Using another port 76, fluid can be delivered to distend the subarachnoid space. Indicia such as 1 mm marks 47 may be placed on the catheter 40 to enhance accuracy of catheter advancement.

Referring to Figure 11, a hollow needle 42 is attached to the polyethylene tubing, being inserted through the endoscope 34 working channel and advanced through the pia mater. The needle 42 includes a side-hole aperture 78, through which the flexible guidewire 80 is advanced out of the needle 42 into the spinal cord 20. The guidewire 80 may have sufficient stiffness to be advanced along a direction extending longitudinally from the side-hole aperture 78. In an exemplary embodiment, the needle 42 is a 30 gauge needle, and the guide wire 80 is a 0.0014" flexible, hollow guide wire dimensioned to advance out of the needle 42, through the side-hole aperture 78. The flexible hollow guide wire 80 is advanced for approximately 15 mm. The guidewire 80 follows a trajectory within the spinal cord 20 that is perpendicular to the side-hole needle 42. The extrusion of the cell trail 22 is commenced as the guidewire is slowly withdrawn.

It is further contemplated that the catheter and needle may be positioned independent of the working channel of the endoscope. In Figure 12A, the injection system and the endoscope are inserted into the patient by way of separate cannulas or introducers 52. The endoscope 34 is positioned through the skin and into the subarachnoid space 50. Using visualization from the endoscope 34, two separate side-hole injection needles 42 are deployed on generally opposite ends of an injured region 26 of the spinal cord 20. The injection needles 42 are positioned to avoid a large vein 82 of the dorsal spinal cord 20. Flexible hollow guidewires 80 extend through the side-hole apertures 78 and into the injured region 26. A cell suspension is ejected from the hollow guidewires 80 as the guidewires 80 are retracted back into the needles 42. As seen in Figure 12B, a trail of cells 22 is formed extending through the injured region 26 of the spinal cord 20.

Clinical Trial

This study employed five cadaveric female pigs weighing approximately 30 kg.

NIH 3T3 fibroblasts were grown in DMEM with 10% fetal bovine serum in a tissue culture flask at 5% CO2 at 37°C. They were labeled with a fluorescent nuclear dye, Hoescht 33342 (Molecular Probes) at a concentration of 1:100. The cells were released from dishes using trypsin and triturated into a suspension. The cell suspension was then centrifuged at 1500 rpm for 5 minutes, the supernatant removed, and L-15 (Gibco) was added to achieve a final concentration of 10^5 cells per µl. The cells were maintained on ice prior to injection.

The lumbosacral anatomy of the adult pig was studied to determine optimal entry points for percutaneous access to the spinal canal. The effectiveness of two flexible endoscopes was compared for this cell injection technique. The MYELOTEC fiberscope (Model 3000E) is designed for lumbar epidural procedures, and offers the advantage of small size (0.9 mm) but its tip is not independently steerable. The scope is deployed by insertion into a disposable 2.7 mm diameter catheter module (Model 4001) with dual Leur-lockable ports and channels. One channel is used to introduce the fiberscope, and the other can be used for irrigation or, for the present invention, insertion of the injection catheter. These ports provide some resistance to fluid back flow, and the introducer also has a valve to also resist fluid back flow. This is advantageous to reduce CSF loss and to maintain fluid distention of the CSF space. The device is "steered" by rotating a disc on the catheter module.

The other fiberscope that was studied was the CODMAN 83340 Neuroguide IOVS. It is a 38 cm long steerable scope of 3.2 mm diameter with a 3 FR working channel. It has a tip articulation of 100-160 degrees, the depth of field is 5-50 mm, and the field of view is 64 degrees in water. Both scopes were deployed in all five animals. For this trial, however, the CODMAN 83340 scope was used for the cellular injections. The endoscopes were coupled to a high resolution color CCD camera (Endoview, Urohealth Systems Inc., Costa Mesa, CA). One video output signal was connected to a monitor, and the second output signal was used to acquire digital video using a Sony DCR-PC100 digital video camera.

To access the lumbar subarachnoid space with the MYELOTEC fiberscope, a 14G spinal needle (2.1mm OD) was directed between L5 and L6, 7 cm rostral to the sacral depression until there was loss of resistance in a glass syringe (epidural space). Next, the dura was penetrated and CSF returned and the depth in mm from the skin to the dural opening was measured. A flexible guidewire was placed through the needle into the subarachnoid space (SAS). The spinal needle was removed and the 7F introducer sheath (2.33 mm OD) was advanced over the guidewire. The guidewire was removed and the catheter module introduced. Next, the 0.9mm (OD) fiberscope was advanced through the catheter module until emergence and visualization of nerve roots was detected. Pulsatile injection of saline through the second channel improved image quality and made it easier to navigate the catheter module and endoscope.

Placement of the CODMAN scope was different than the MYELOTEC fiberscope because of its greater size. A 12.5F peel-away introducer was fed over a large (10G, OD

= 3.4mm) needle placed into the SAS at L5/6. The needle was then removed and the endoscope introduced into the SAS through the sheath. A large syringe (30cc) was attached via a three-way stopcock to the working channel port and small pulses of saline were injected. Both endoscopes were navigated adjacent to the dorsal or dorsolateral spinal cord surface. Because the CODMAN introducer does not have a valve to prevent backflow, more fluid was used to distend the subarachnoid space since there was a constant loss of fluid through the small gap between the scope and the introducer.

All cellular injections described hereinafter were delivered using the CODMAN endoscope. Injection was performed in a dorsal midline area at the L2 vertebral level. Thirty-six µl of the cell suspension was loaded into a polyethylene tube [0.61 mm OD, 0.28 mm ID] 58cm in length (Intramedic polyethylene tubing PE-10) with a 30G needle (8mm total length, OD 0.3mm) attached at its distal end. Fluid infusion was stopped, and the catheter was slowly inserted into the working channel and advanced distally until the needle tip could be visualized to exit the endoscope. It was then necessary to rotate the endoscope to optimize the relative positions of the optical fiber bundle, the needle, and the dorsal spinal cord. With the scope facing the dorsal spinal cord surface at a 45 degree angle, the needle was advanced until it contacted the pial surface.

Following pial perforation, the needle was advanced 4mm along a rostro-ventral trajectory by gently pushing the catheter into the endoscope. At this point irrigation was terminated with the subarachnoid space moderately distended at a pressure of 30-35 cm H_2O. One µl of cell suspension was injected, and another 4 ul was injected while the needle was slowly withdrawn from the cord over about 5 minutes. Then, the needle was left in position for a further two minutes before being removed from the spinal cord parenchyma. No further pulses of saline irrigation were delivered in order to minimize the possibility of flushing the cells along the neural axis. The endoscope was removed and 4% paraformaldehyde was slowly infused into the subarachnoid space around the injection site. A lumbar laminectomy was then performed to remove the injected region of the spinal cord for histological evaluation.

In preparation for histological assessment, the specimens were post-fixed in 4 percent paraformaldehyde for two weeks. The cord was embedded in gelatin and cut into 55µm sagittal sections using a sliding freezing microtome. The sections were visualized using a Zeiss Axiophot fluorescent microscope to identify the fluorescent-labeled injected cells. Digital images were acquired at 10x using METAMORPH software. Image

montages were constructed in ADOBE PHOTOSHOP 5.0 to show the full length of the cellular trail within the spinal parenchyma and to assess for spillage at the adjacent spinal cord margins.

A useful anatomic landmark in the pig is a palpable sacral depression (SD) from which the L5/6 interspace was located 7 cm rostrally. The vertical distance from the skin to the dorsal surface of the cord at L5/6 was 6-7 cm. The interlaminar spaces (or lumbosacral interspaces) at L5-6 and L6-S1 at the midline were 4.0 and 2.5mm respectively. The porcine conus medullaris terminates within the sacrum 3 cm rostral to the SD, thus there is no true lumbar cistern as in the human.

Video image quality was similar using either the MYELOTEC or CODMAN endoscopes. Blood vessels, nerve roots, and denticulate ligaments could be visualized with either endoscope. Adequate visualization of anatomic details during scope navigation required pulsatile irrigation of the subarachnoid space with fluid. Although the size of the CODMAN scope was greater, the ability to control the direction of the injection needle and catheter was better than with the disposable MYELOTEC catheter module. This appeared to be due to stiffness within the scope tip and the fact that the CODMAN scope was only actively directable at the tip. The steering motion of the MYELOTEC scope was more whip-like and it tended to flip from the midline to the lateral spinal canal during attempted injections. For this reason, the CODMAN endoscope was utilized for definitive injections.

A useful feature of this technique is that while the tubing and at least part of the needle are within the scope, the needle behaves as a rigid extension of the scope. This allows for the force necessary to penetrate the pial surface. When a loop of tubing is fed out between the tip of the scope and the needle after insertion into the cord, small motions of the scope and spinal cord are damped with respect to the needle. This has the effect of reducing injection-associated spinal cord trauma by allowing the needle to move with the spinal cord during physiologic motion.

Trial Results

During histological analysis, a trail of Hoechst-labeled cells was identified in each specimen under a fluorescent microscope. Some trails were homogenously distributed whereas others consisted of interspersed clumps of labeled cells. Some cell spillage was evident on the adjacent pia in 4/5 specimens; however, cells were not seen more than 3

mm from the injection site, and neither traumatic distention of the central canal nor cavitation as a result of the injection was observed.

The development of small flexible fiberoptic scopes and high resolution CCD cameras has lead to increased interest in the use of endoscopes for spinal canal applications. Multiple injections into the spinal cord over an extended time period may be necessary for effective regeneration. The technique described herein could also be used to deliver non-cellular biomaterials into the subarachnoid space or spinal cord. Alternatively, other therapeutic effects, such as pain modulation via chromaffin cells transplanted into the subarachnoid space might be achieved with this technique.

Due to camera and display interface associated degradation, an alternative consideration is to use rigid endoscopes with their superior rod lens optics. A technique based on a rigid endoscope would sacrifice some of the advantages of the flexible scope such as entry into the subarachnoid space at a point several segments distal to the injection site and the flat injection trajectory possible by having the flexible scope nearly parallel to the spinal cord. The incorporation of backflow resistance valves into the MYELOTEC introducer and catheter module means that less fluid volume needs to be delivered to distend the subarachnoid space than with the CODMAN introducer where some constant backflow occurs. However, the advantage of not incorporating a valve is that CSF pressures are less likely to be escalated using the CODMAN introducer and endoscope. Using a porcine model of subdural fluid infusion, it has been shown that spinal cord ischemia occurs at induced CSF pressures of approximately 65 mm Hg.

While dural puncture is simple with a spinal needle, getting flexible introducers to enter the porcine dural sheath over a guidewire requires more effort. Therefore, a large spinal needle was used to improve the ability to pass the CODMAN guide sheath through the dura. In clinical application of the 7F MYELOTEC introducer for intradural procedures, there have not been CSF leaks.

The concept of creating cellular trails to guide regenerating axons assumes that cellular migration following transplantation is minimal. Random cellular migration could lead to poorly organized or misdirected axonal growth. In a previous study trails of Schwann cells were not dispersed 6 weeks after injection. Axons grew along the trails in a fasciculated pattern similar to that seen in peripheral nerve grafts. The injection technique utilized in this trial appeared to cause little injury to the spinal cord.

Percutaneous endoscopic cellular injection may be useful for cellular transplantation, may reduce surgical and anesthetic time, be compatible with local

anesthesia, eliminate the need to disrupt spinal instrumentation and bone grafts, and allow greater flexibility in the respective timing of spinal fixation and cellular transplantation following spinal cord injury. Using the system and method according to the present invention, intraspinal cellular injection using a flexible endoscope from a percutaneous access is achievable.

All references cited herein are expressly incorporated by reference in their entirety.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described herein above. In addition, unless mention was made above to the contrary, it should be noted that all of the accompanying drawings are not to scale. Accordingly, a variety of modifications and variations are possible in light of the above teachings without departing from the scope and spirit of the invention. For example, the invention has been described with reference to a spinal cord procedure. It should be appreciated that the present invention can be applied to a number of situations in which percutaneous introduction of cells or other biomaterial is desired.

What is claimed is:

1. A method for treating an injury of a spinal cord of a patient, the method comprising implanting a therapeutic substance in the spinal cord under indirect visualization.

2. The method of claim 1 wherein the indirect visualization is provided by an endoscope.

3. The method of claim 2 further including inserting the endoscope through a skin puncture site remote from the injury of the spinal cord.

4. The method of claim 3 wherein a distal portion of the endoscope is positioned in an interlaminar space of the patient.

5. The method of claim 4 wherein implanting the therapeutic substance includes inserting an injection member through the skin puncture site and into the spinal cord.

6. The method of claim 5 wherein implanting the therapeutic substance includes injecting the therapeutic substance through an aperture of the injection member.

7. The method of claim 6 wherein implanting the therapeutic substance includes at least partially withdrawing the injection member from the spinal cord while injecting the therapeutic substance to thereby form a trail of the therapeutic substance.

8. The method of claim 7 wherein a magnetic resonance imaging reflective material is implanted along with the therapeutic substance.

9. The method of claim 8 wherein implanting the therapeutic substance is performed under magnetic resonance imaging.

10. The method of claim 7 wherein the injection member is slideably disposed in a working channel of the endoscope.

11. The method of claim 10 wherein the injection member includes a needle connected to a catheter, a distal portion of the needle being inserted into the spinal cord.

12. The method of claim 11 further including absorbing motion of the needle in the spinal cord relative to the endoscope by providing a flexible portion of the catheter between the needle and a distal end of the endoscope.

13. The method of claim 7 wherein the therapeutic substance includes cells.

14. The method of claim 13 further including injecting distention fluid in the interlaminar space.

15. The method of claim 5 wherein the injection member includes a needle with a side-hole aperture, a catheter connected to the needle, and a flexible hollow guidewire slideably disposed in lumens of the catheter and needle and through the side-hole aperture of the needle.

16. The method of claim 15 wherein implanting the therapeutic substance includes positioning a distal portion of the hollow guidewire within the spinal cord.

17. The method of claim 16 wherein implanting the therapeutic substance includes injecting the therapeutic substance from the hollow guide wire while the guide wire is being withdrawn from the spinal cord to thereby form a trail of therapeutic substance in the spinal cord.

18. The method of claim 17 wherein the therapeutic substance includes cells.

19. A spinal cord injury treatment device comprising:
visualization means for visualizing a spinal cord through a skin puncture located remote from an injury site of the spinal cord; and
injection means for injecting a therapeutic substance into the spinal cord.

20. The device of claim 19 wherein the visualization means includes an endoscope.

21. The device of claim 20 wherein the endoscope and injection means are configured for insertion in an interlaminar space of the patient.

22. The device of claim 21 further including means for withdrawing the injection means while injecting the therapeutic substance to thereby form a trail of the therapeutic substance in the spinal cord.

23. The device of claim 22 wherein the means for withdrawing includes a catheter advancement member.

24. The device of claim 22 wherein the therapeutic substance includes a magnetic resonance imaging reflective material.

25. The device of claim 19 wherein the injection means includes a needle connected to a catheter, the needle having an aperture and the needle configured for at least partial insertion into the spinal cord.

26. The device of claim 25 wherein the injection means is configured for slideable insertion into a working channel of an endoscope.

27. The device of claim 26 wherein the catheter includes a flexible portion between the needle and endoscope, the flexible portion configured and dimensioned to dampen motion of the needle relative to the endoscope.

28. The device of claim 19 further including means for fluid distention.

29. The device of claim 28 wherein the means for fluid distention includes a syringe connected with an endoscope.

30. The device of claim 22 wherein the therapeutic substance includes cells.

31. A spinal cord injury treatment device comprising:

visualization means for visualizing a spinal cord through a skin puncture located remote from an injury site of the spinal cord; and

first and second injection means for injecting a therapeutic substance into the spinal cord.

32. The device of claim 31 wherein the visualization means includes an endoscope, a distal portion of the endoscope configured and dimensioned for insertion into an interlaminar space of the patient.

33. The device of claim 32 wherein the first and second injection means each include a needle connected to a catheter and a flexible hollow guidewire slideably disposed with a lumen of the needle and catheter.

34. The device of claim 33 wherein each needle includes a side-hole aperture.

35. The device of claim 34 wherein distal portions of each guide wire are dimensioned and configured for insertion into the spinal cord.

36. The device of claim 35 wherein distal portions of each flexible hollow guide wire are configured for ejecting the therapeutic substance.

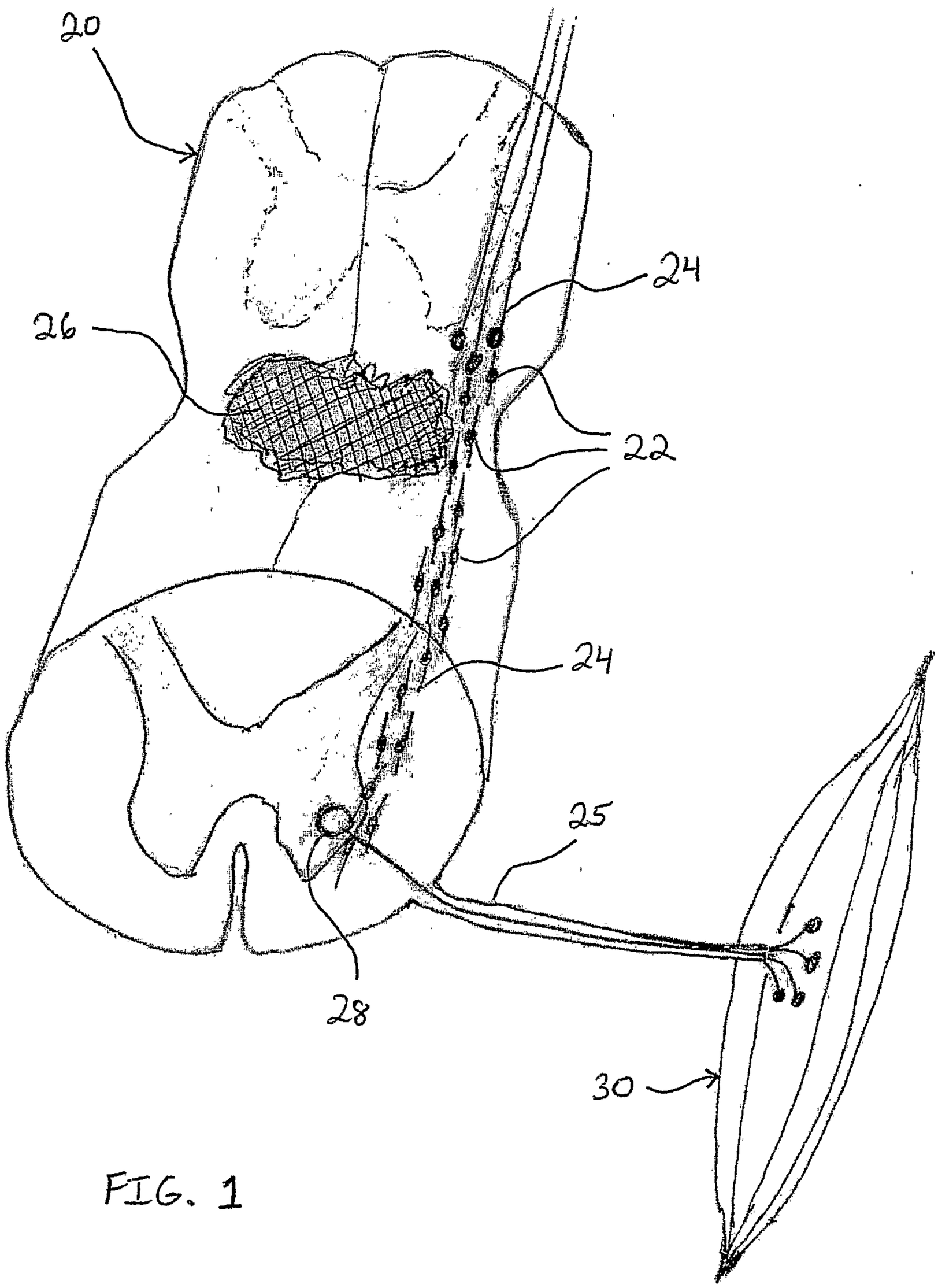


FIG. 1

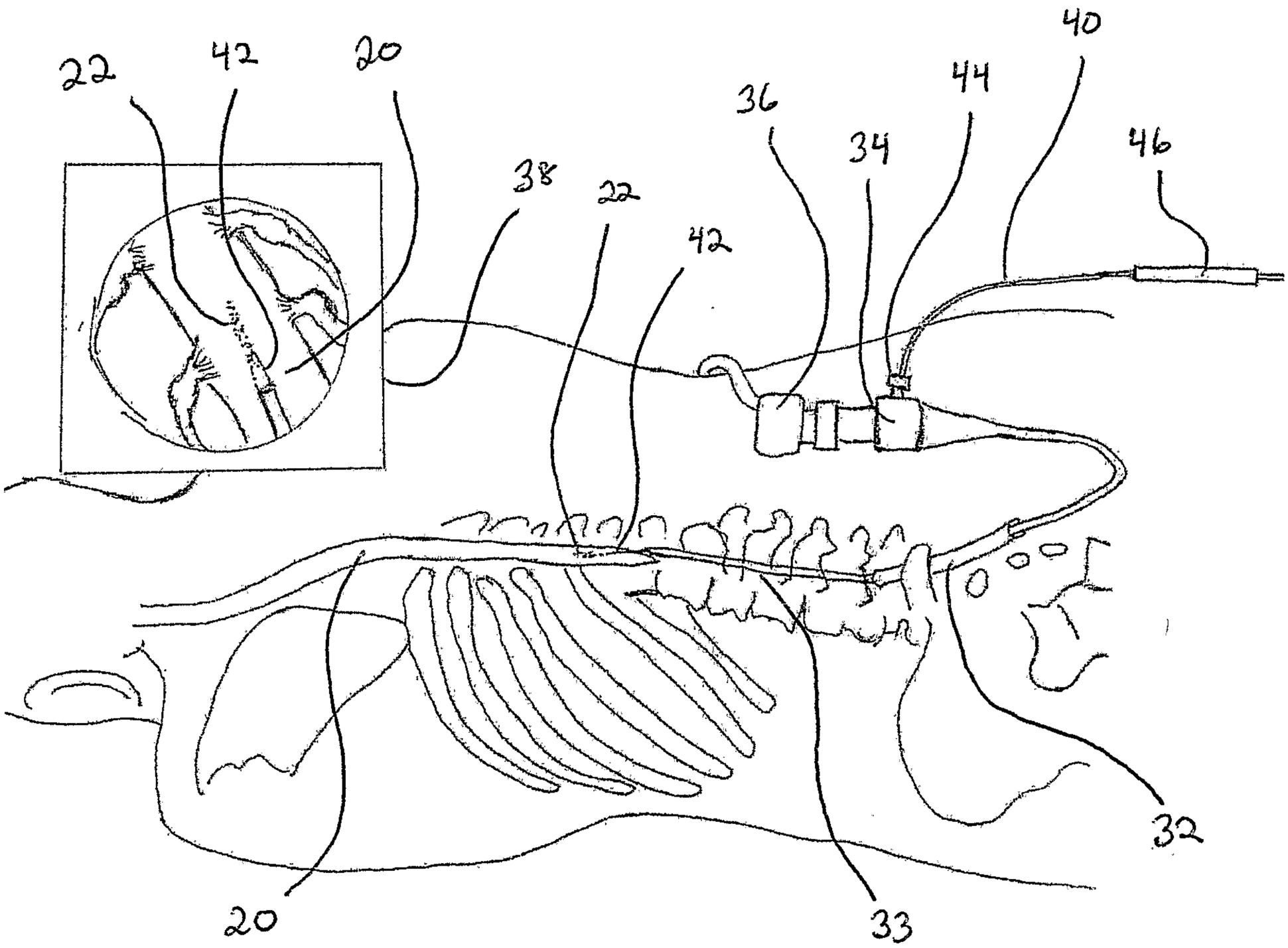


FIG. 2

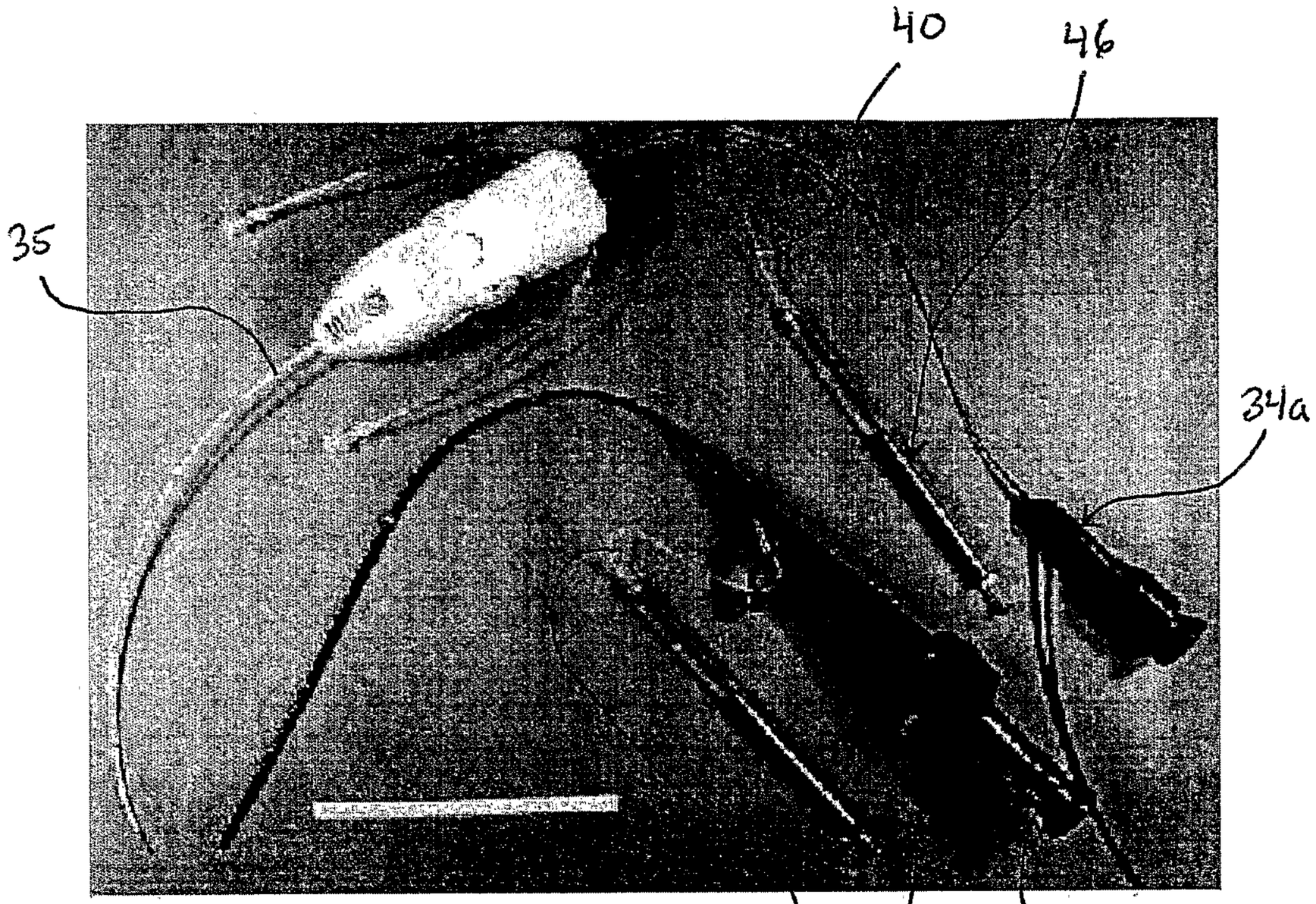


FIG. 3A

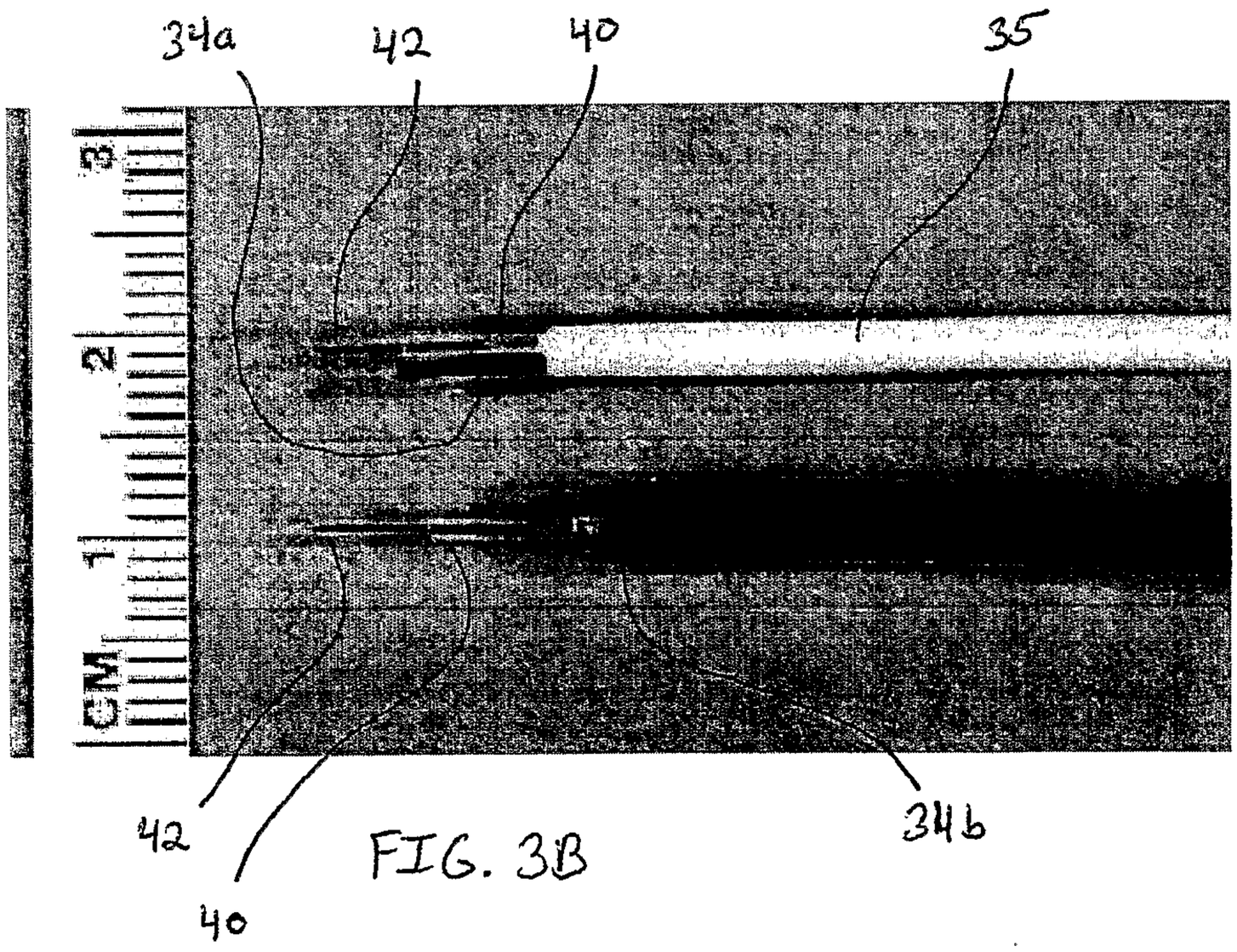


FIG. 3B

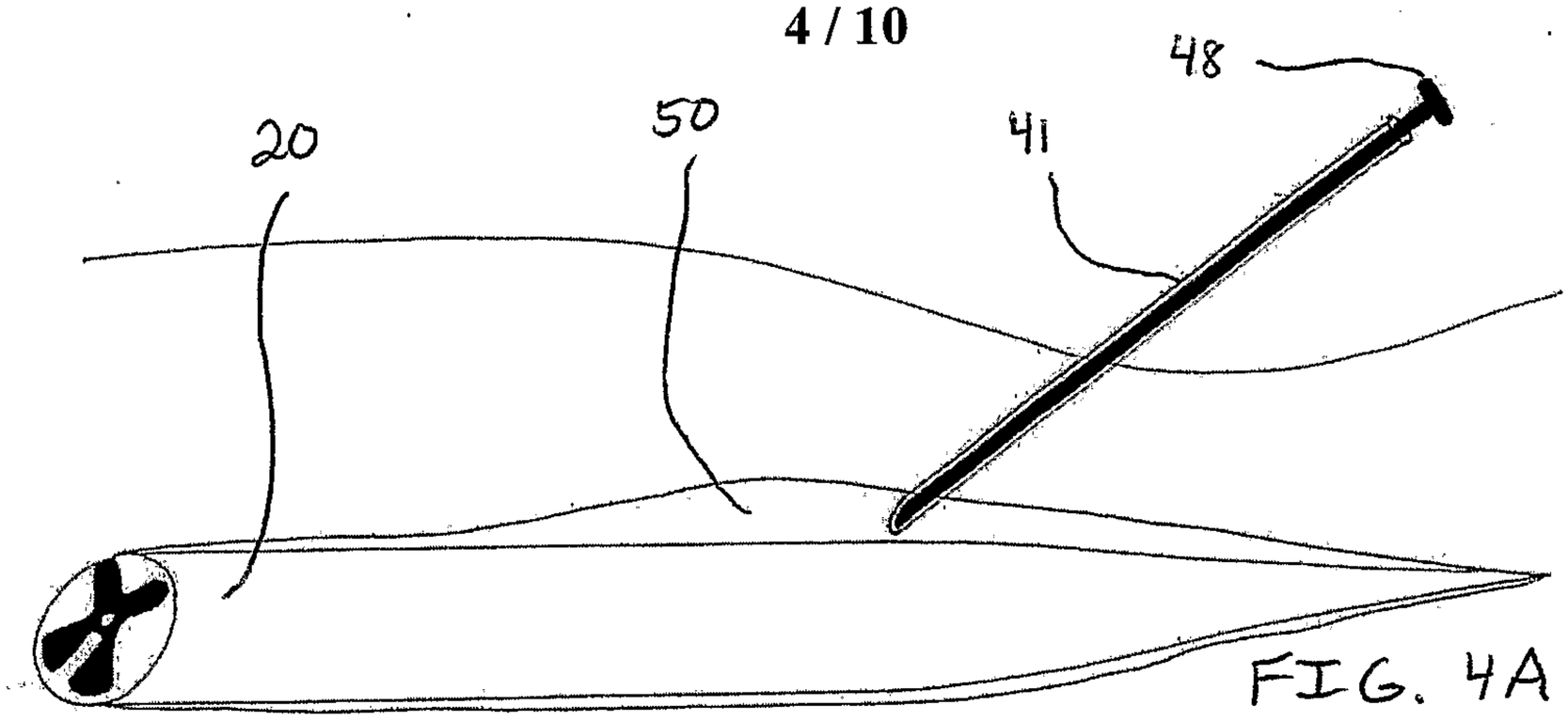


FIG. 4A

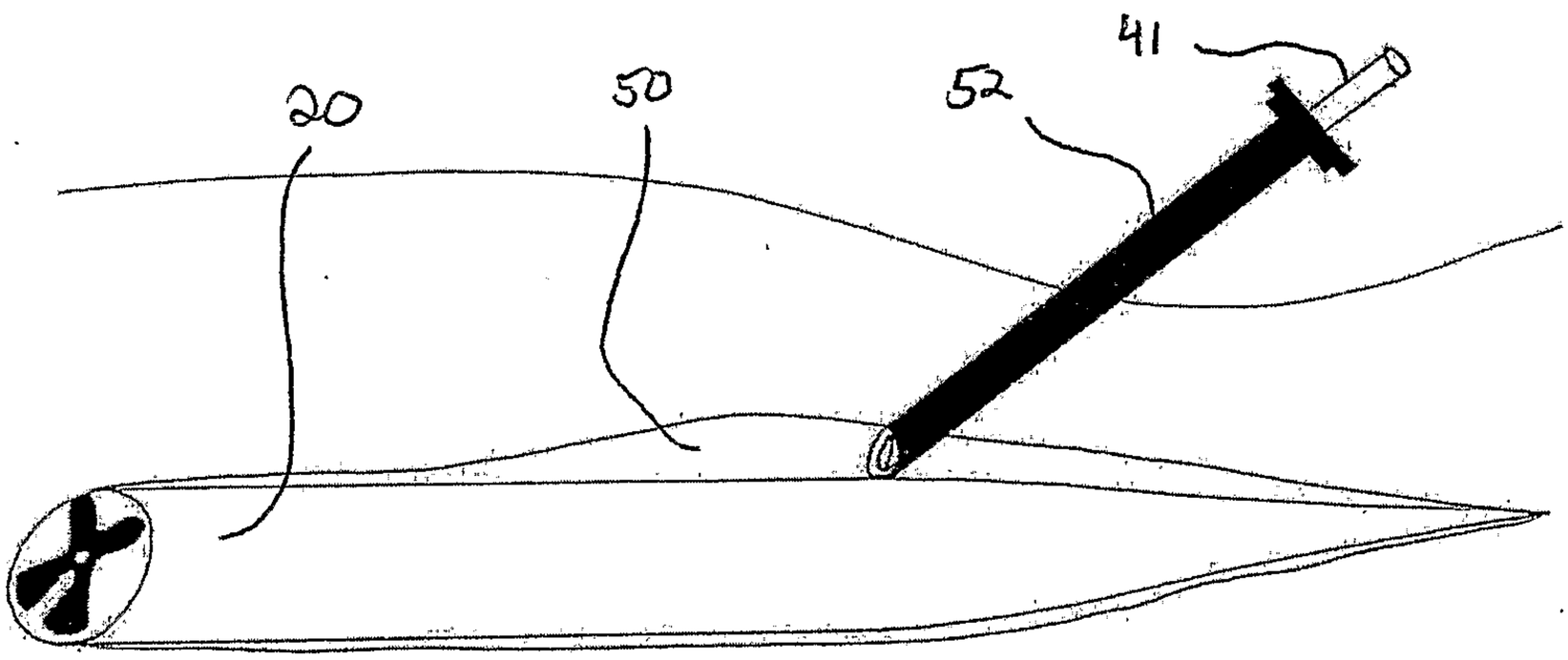


FIG. 4B

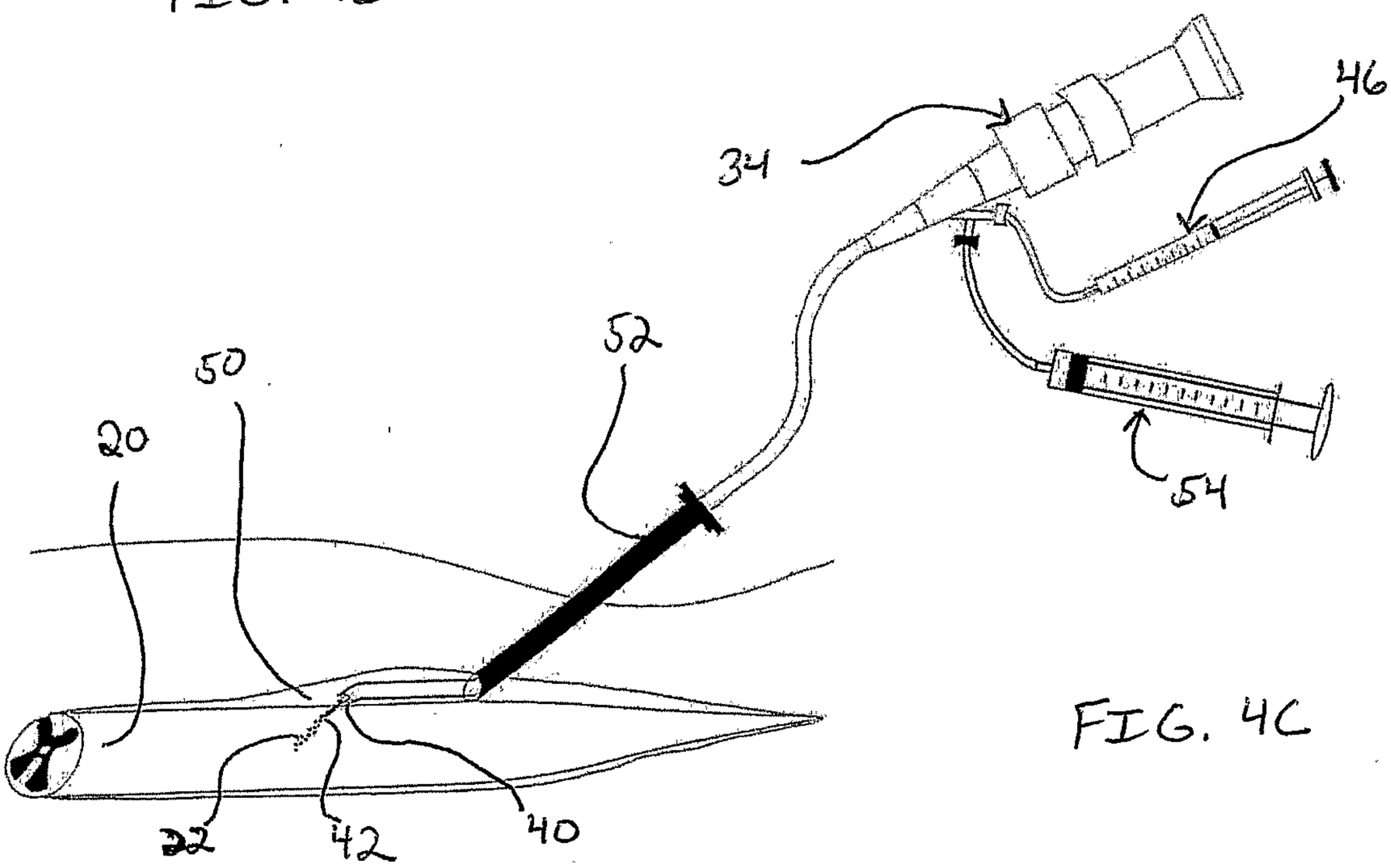


FIG. 4C

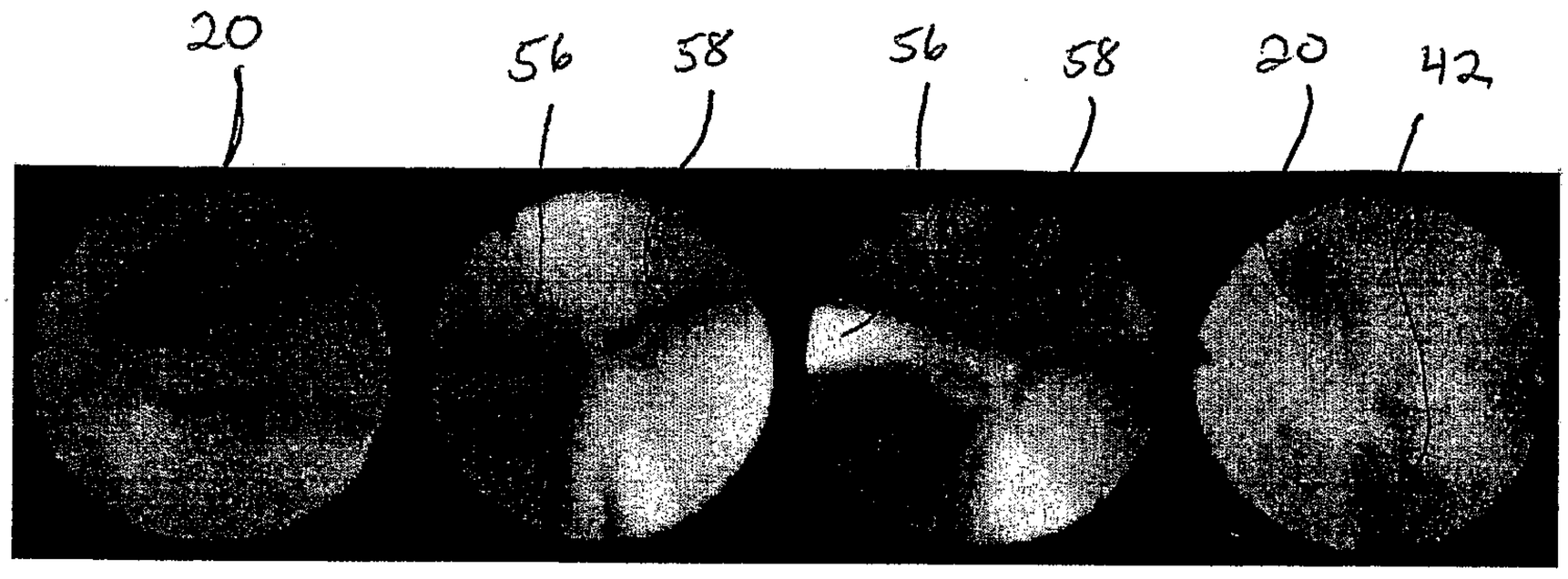


FIG. 5A FIG. 5B FIG. 5C FIG. 5D

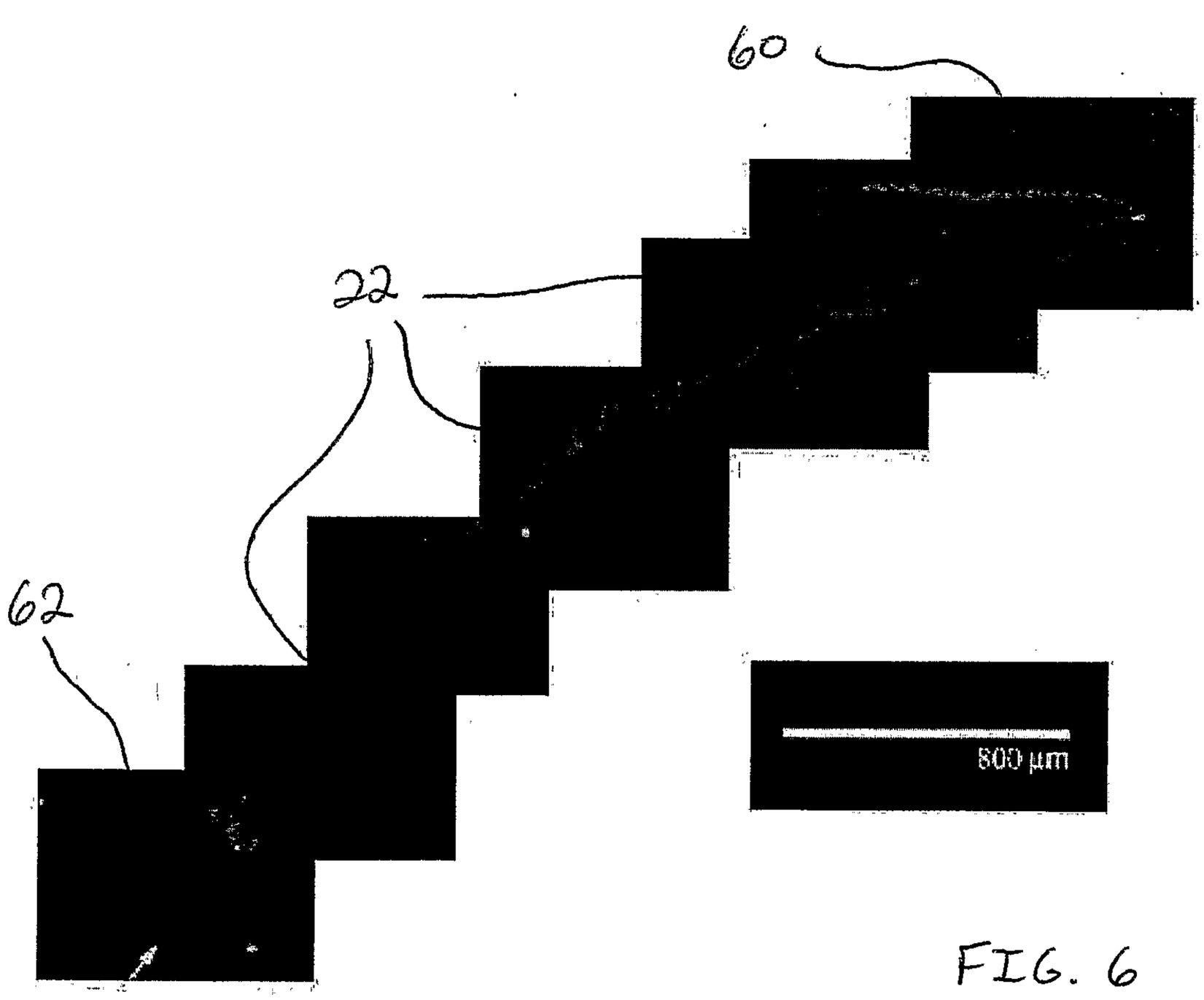


FIG. 6

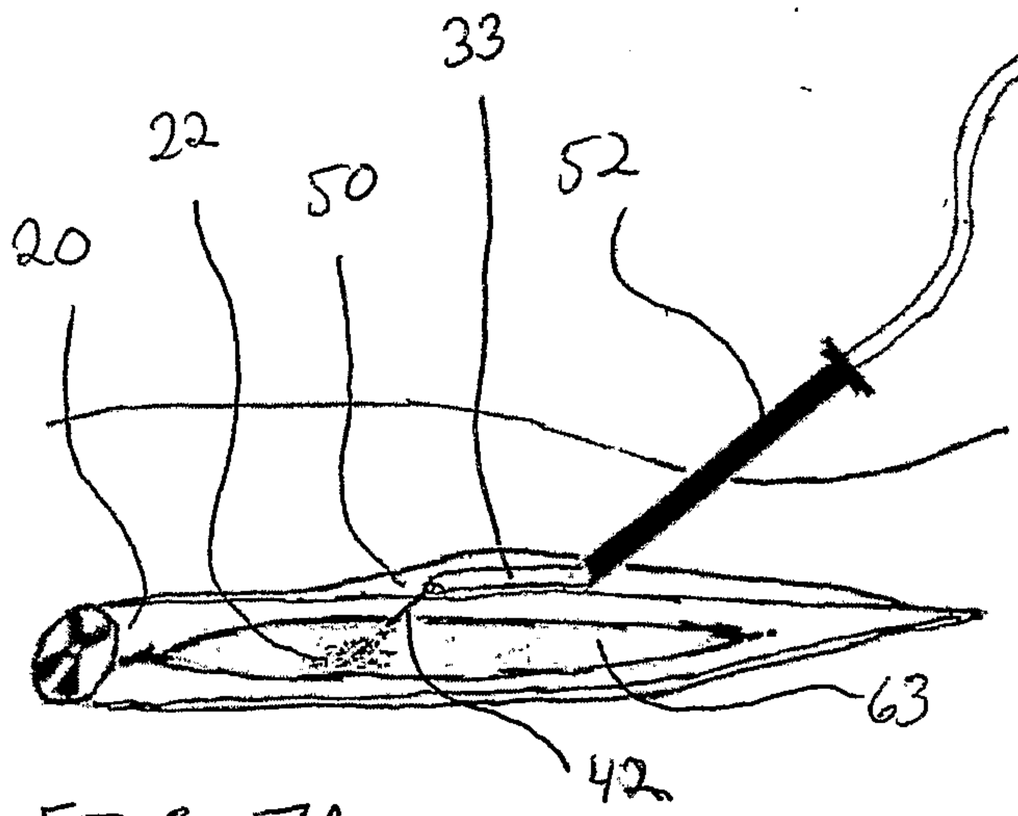
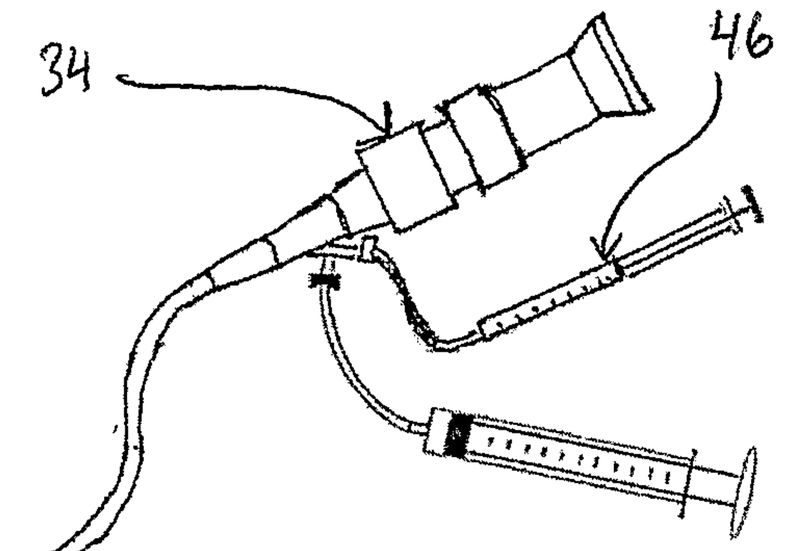


FIG. 7A



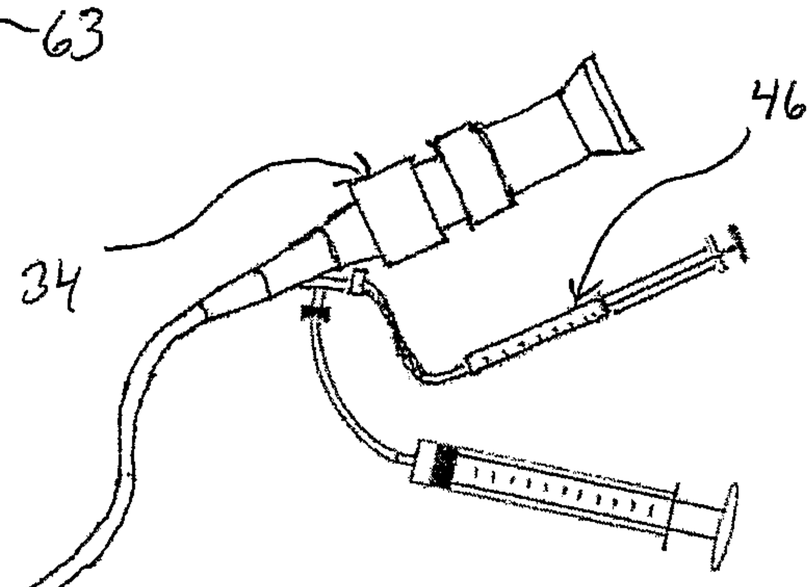


FIG. 7B

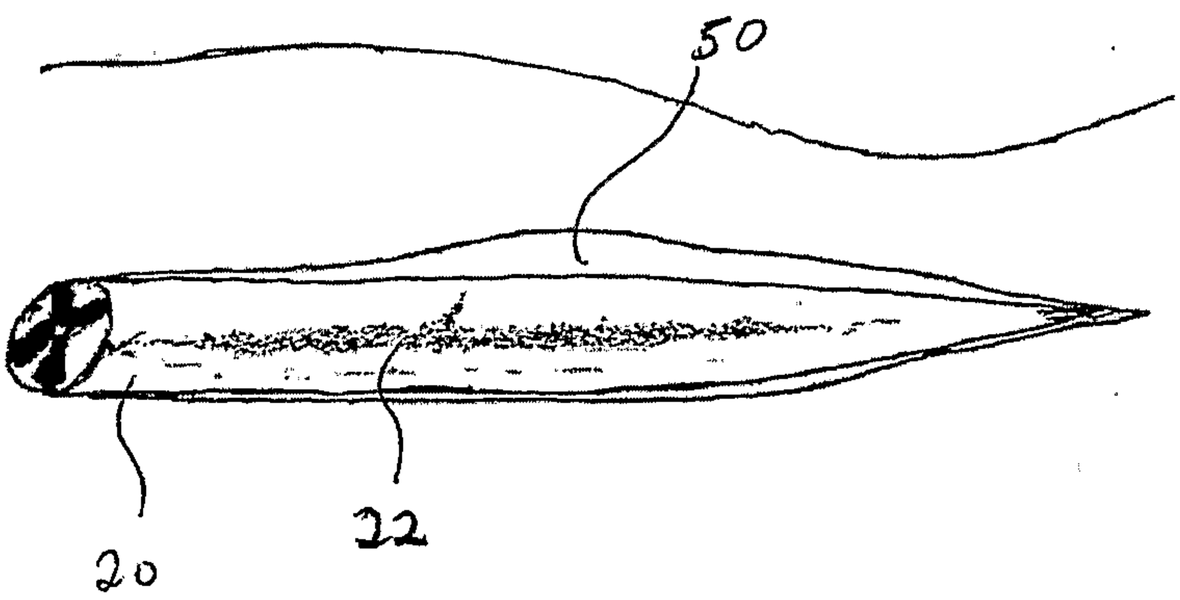


FIG. 7C

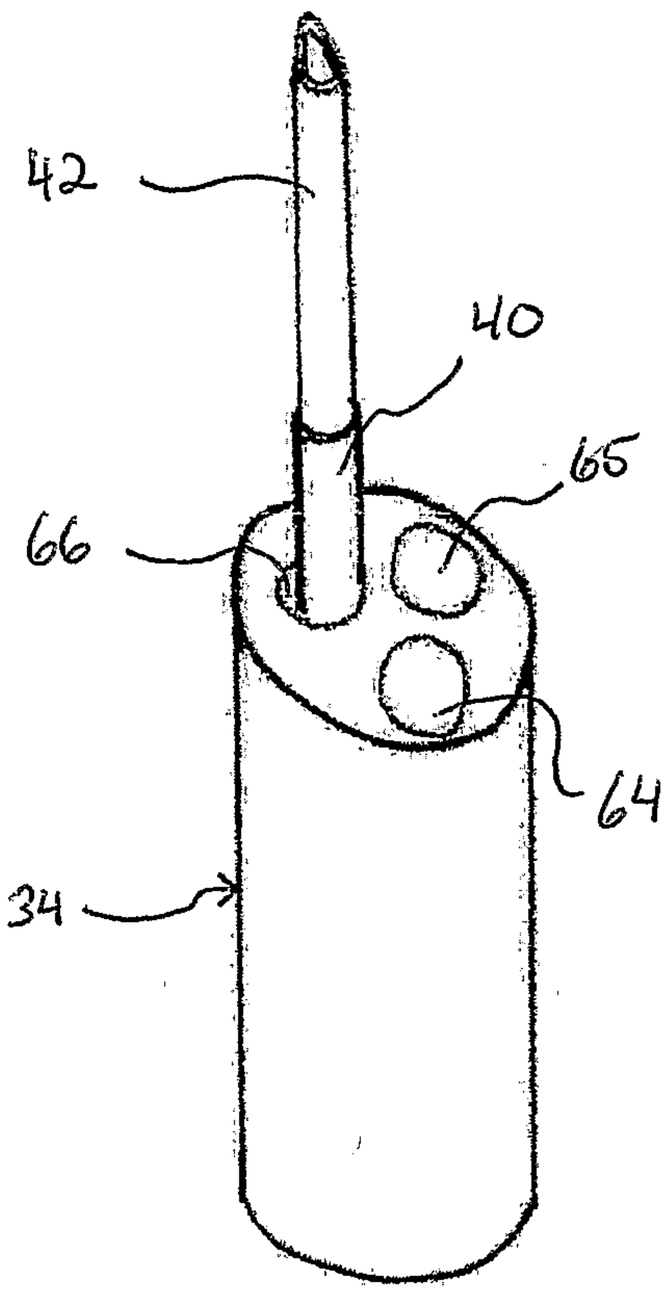


FIG. 8

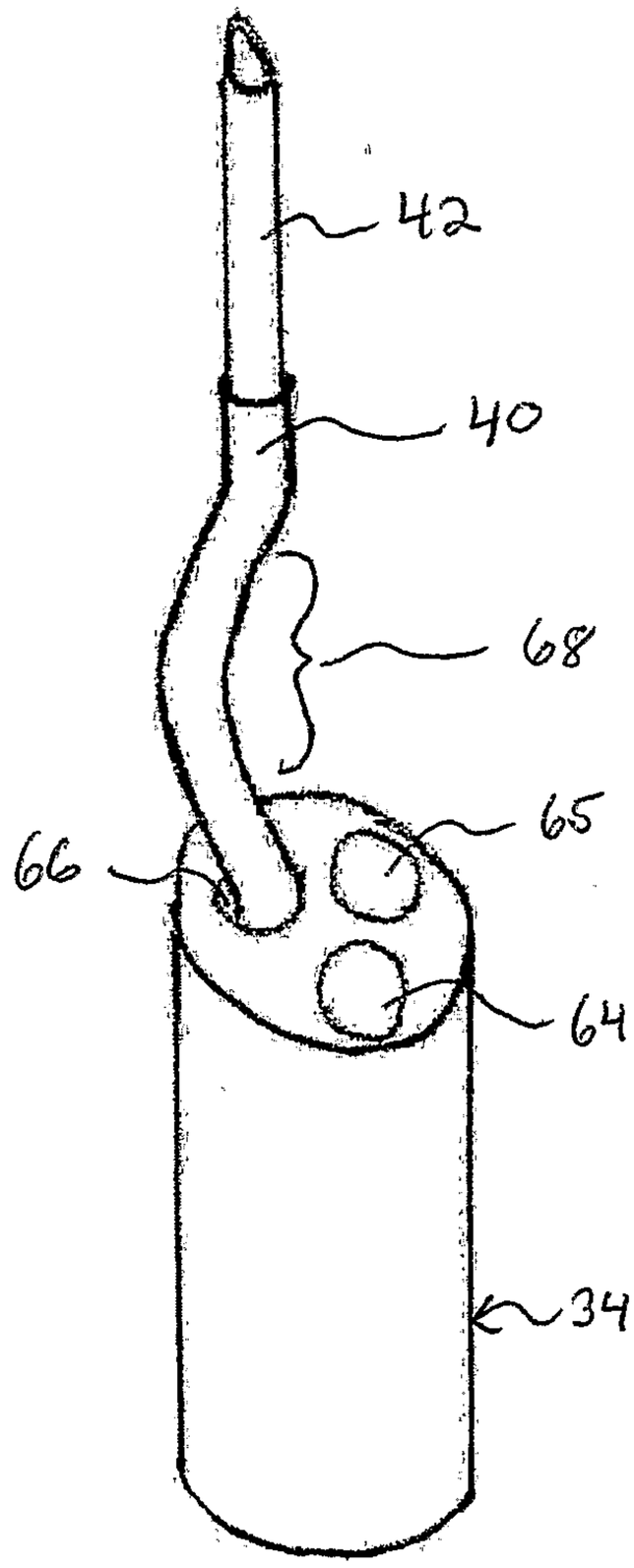


FIG. 9

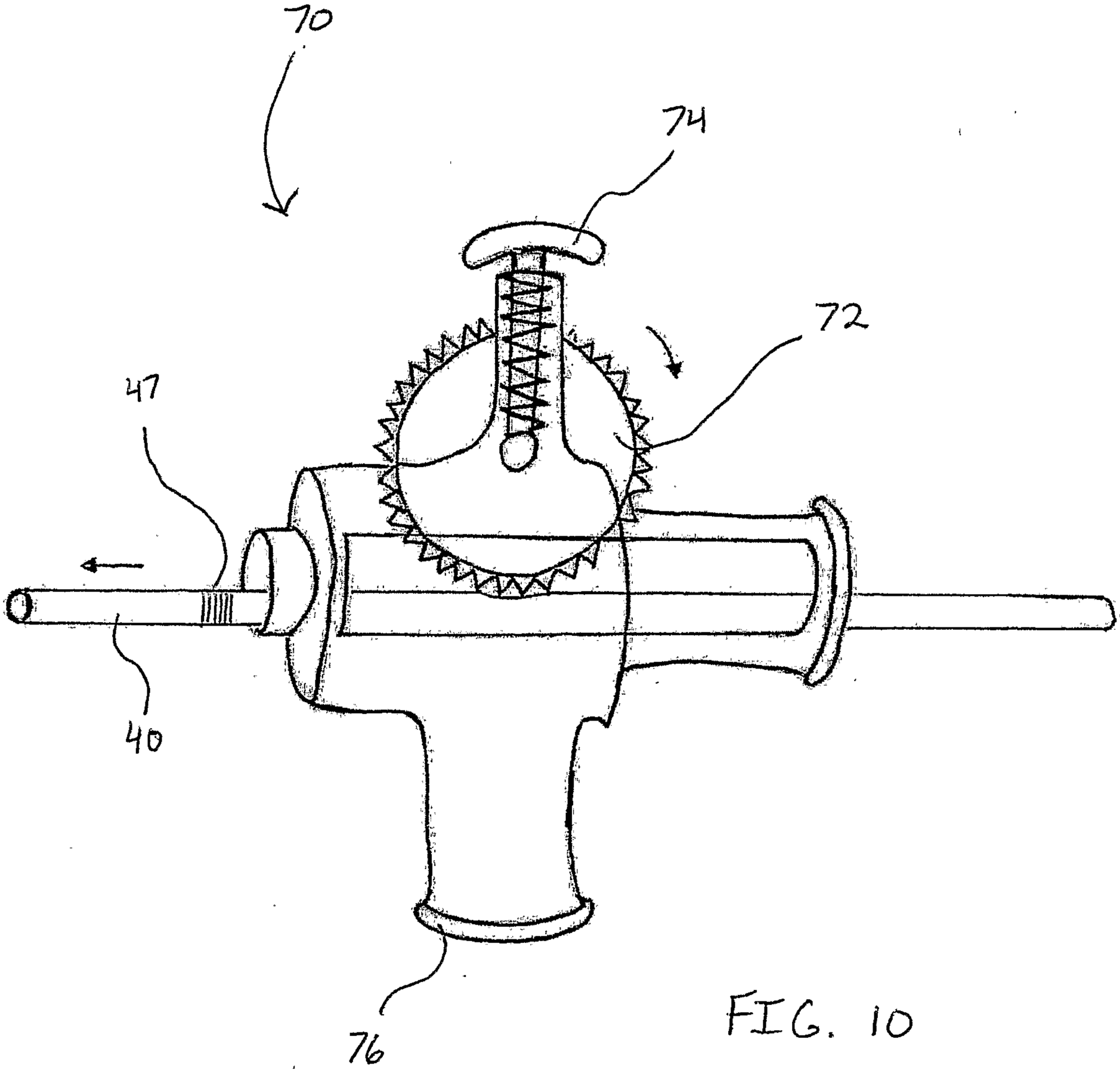


FIG. 10

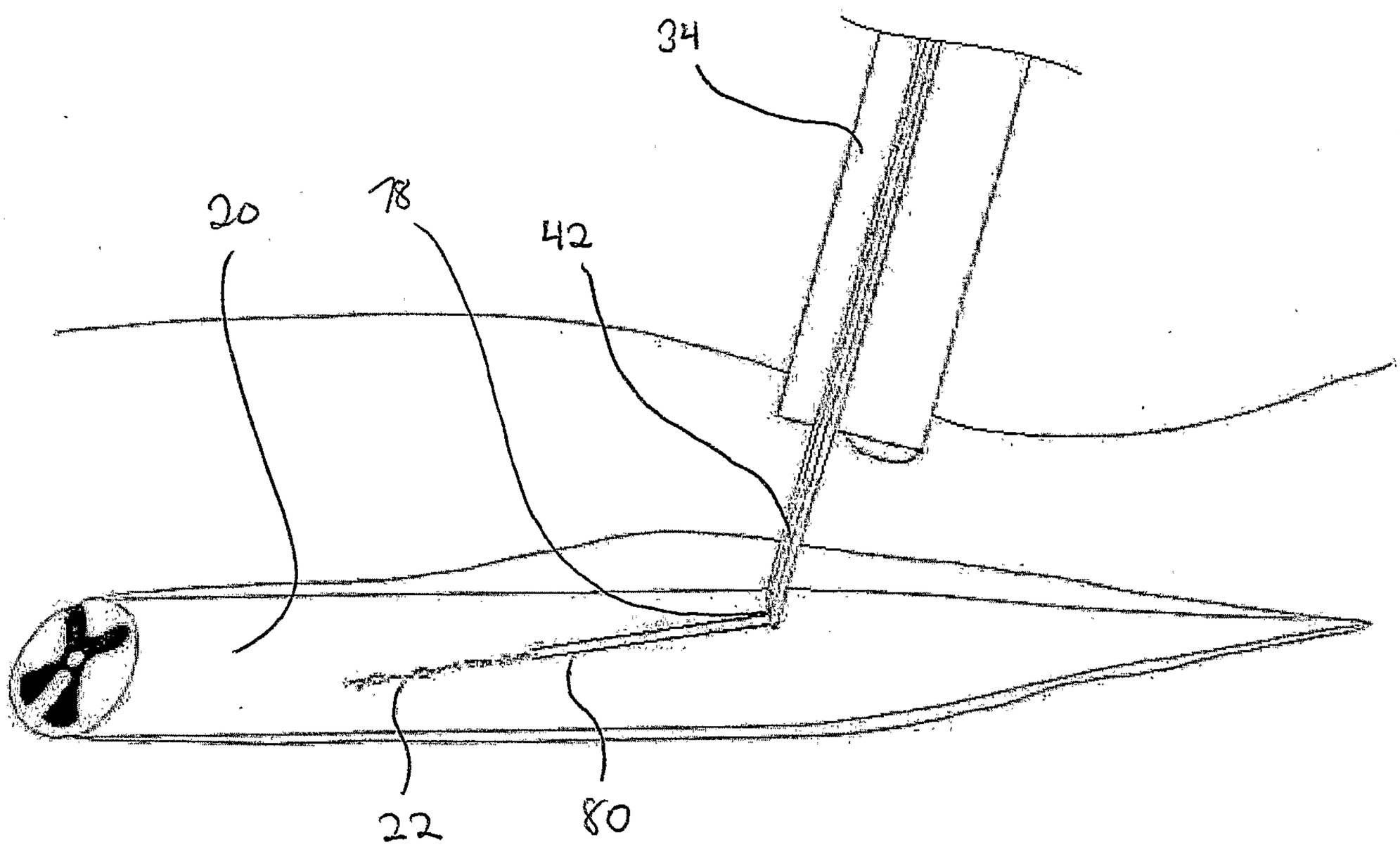


FIG. 11

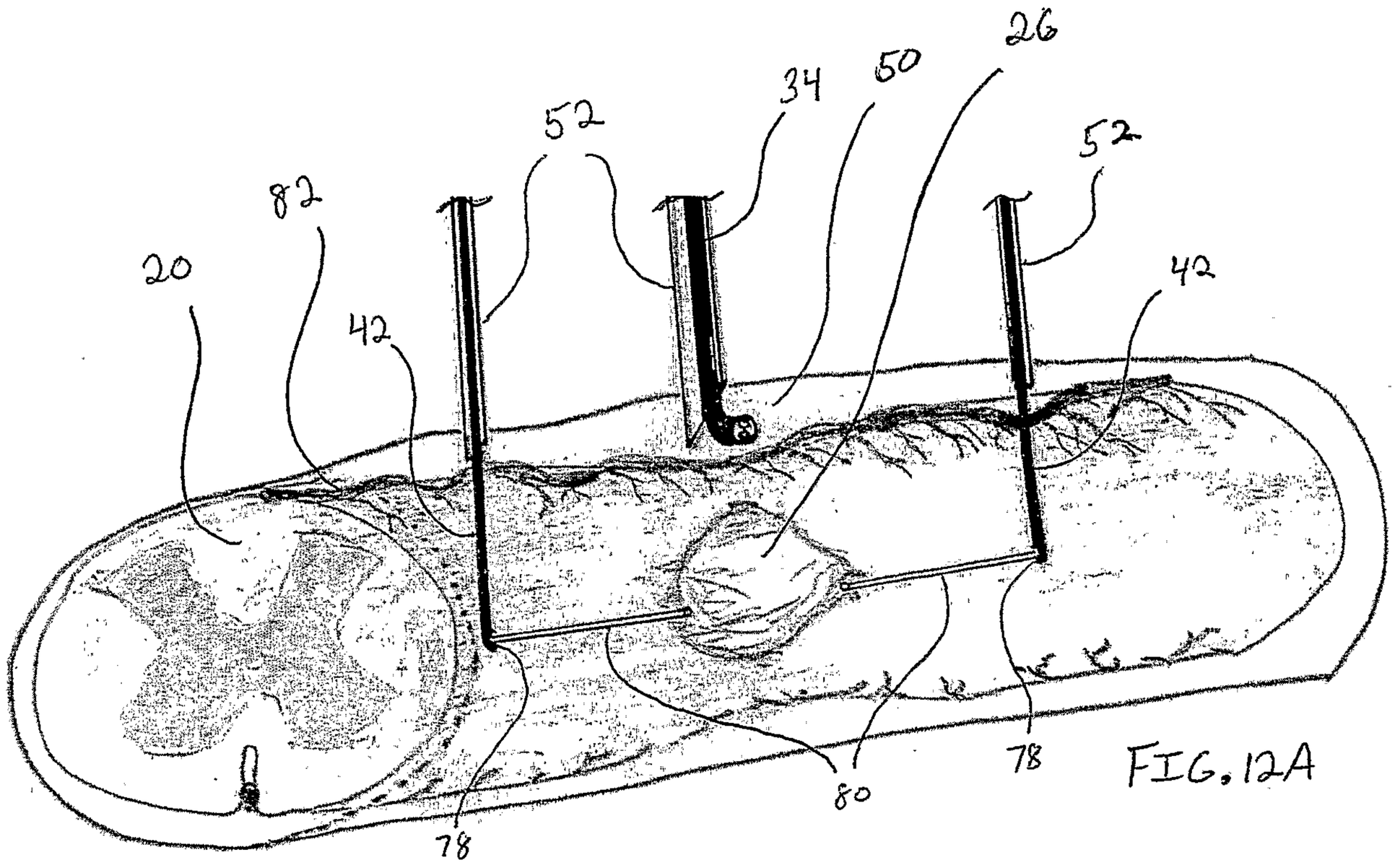


FIG. 12A

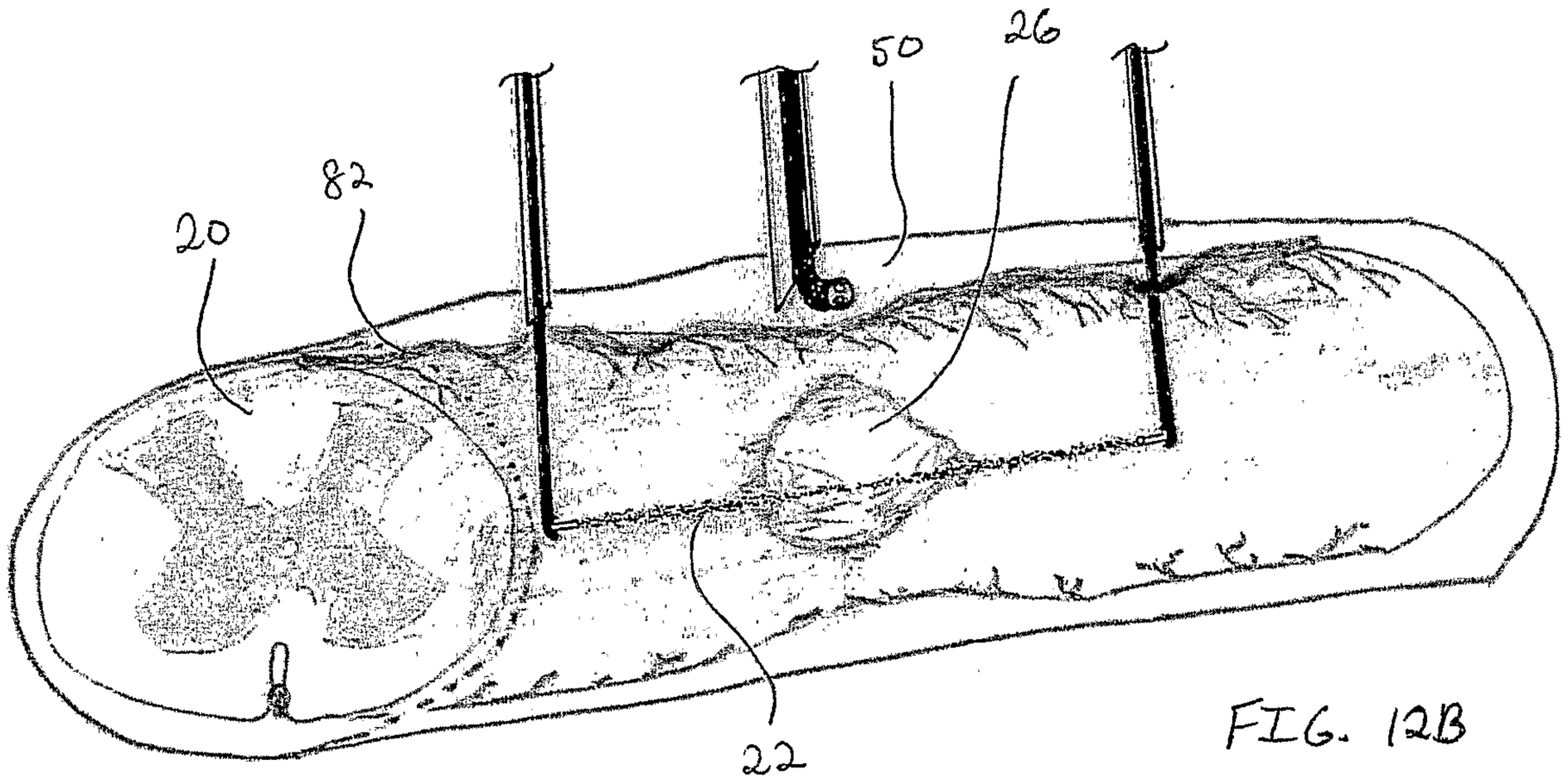
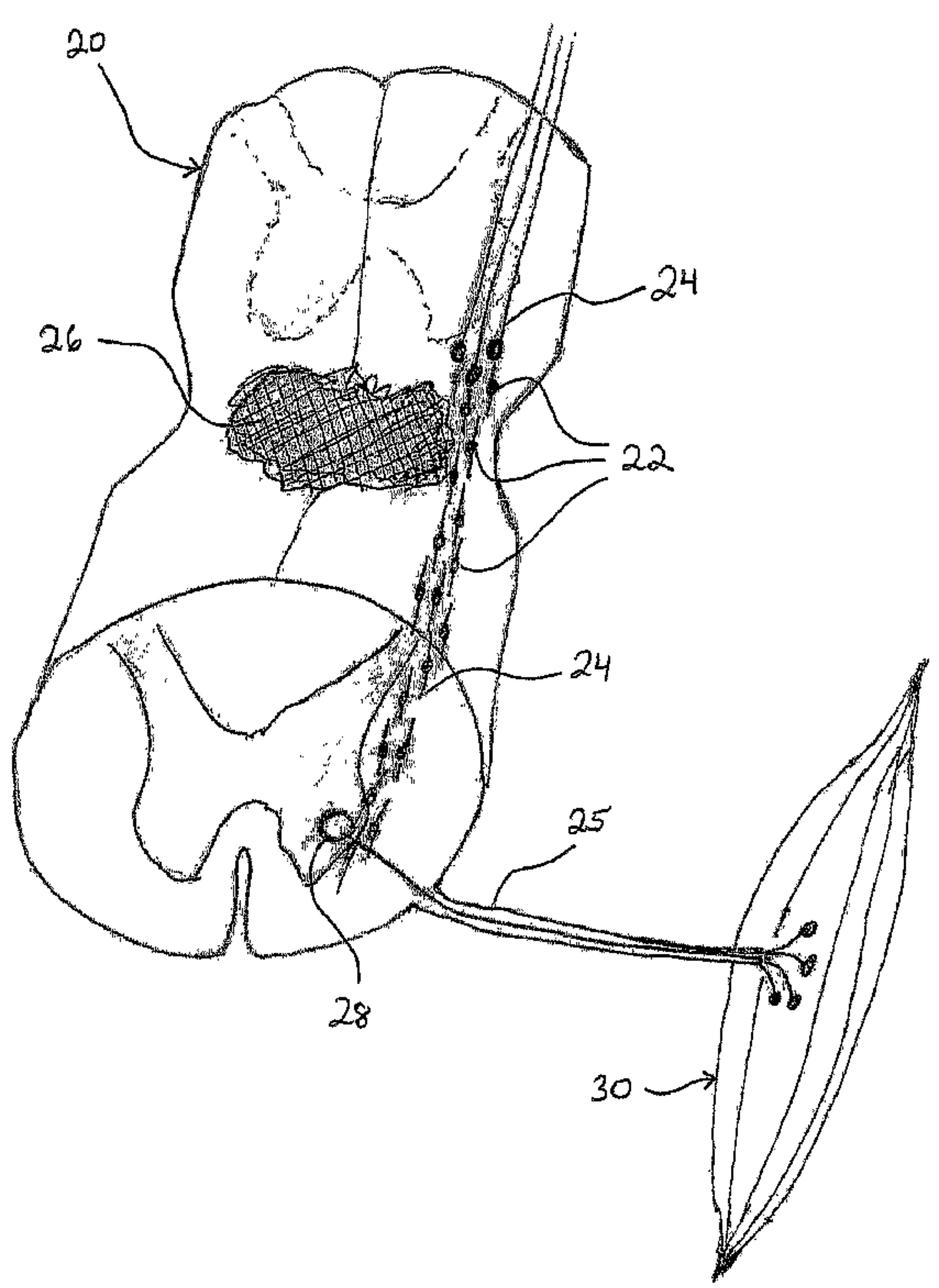


FIG. 12B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