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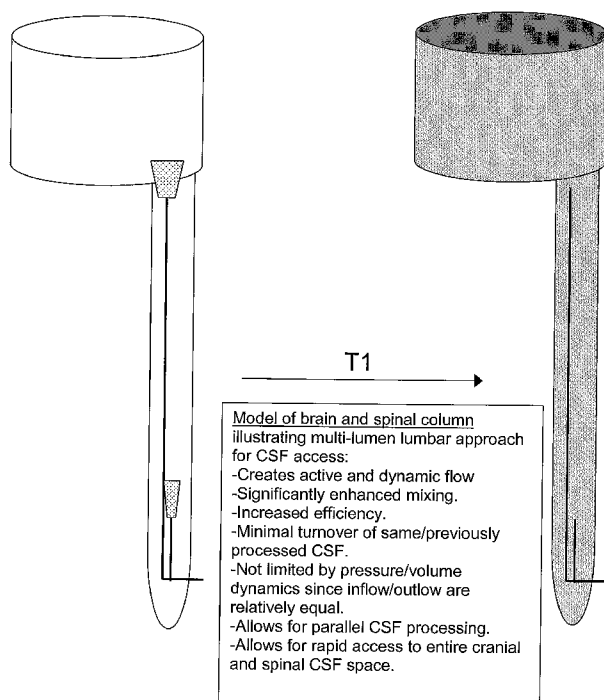
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(54) Title: CEREBROSPINAL FLUID PURIFICATION SYSTEM

Figure 8A



(57) Abstract: The present invention provides methods and systems for conditioning cerebrospinal fluid (CSF). The methods provide for efficiently removing target compounds from CSF. The systems provide for a multilumen flow path and exchange of a majority volume portion of CSF in the CSF space. The removal and/or delivery of specific compounds can be tailored to the pathology of the specific disease. The removal is targeted and specific, for example, through the use of specific size-exclusion thresholds, antibodies against specific toxins, and other chromatographic techniques, as well as delivery and/or removal of targeted therapeutic agents. The invention finds use as a diagnostic, therapeutic and drug delivery platform for a variety of diseases affecting the CNS by accessing the CSF space. Exemplified disease conditions treatable by the present CSF processing systems and methods include, but are not limited to: Cerebral Vasospasm, Guillain Barre Syndrome, Alzheimer's, Parkinson's, Huntington's, Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Spinal Cord Injury, Traumatic Brain Injury, Stroke, Cancer affecting the brain or spinal cord, Prion disease, Encephalitis from various causes, Meningitis from various causes, diseases secondary to enzymatic or metabolic imbalances, Biological Warfare, etc. For the first time, the present invention offers patients a disease-modifying, disruptive technology treatment platform that addresses the known disease pathogenesis of a number of neurologic conditions to which there are presently limited and ineffective treatment options.



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CEREBROSPINAL FLUID PURIFICATION SYSTEM

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Application No. 60/828,745, filed on October 9, 2006, the entire disclosure of which is hereby incorporated herein by reference for all purposes.

FIELD OF THE INVENTION

[0002] The invention pertains generally to medical devices and methods. More particularly, the present invention relates to devices, systems methods and kits for removal of toxins from the cerebrospinal fluid (CSF). More specifically, the method and system can be used to diagnose and treat disorders affecting the central nervous system (CNS) by measuring and modifying the chemical composition of CSF.

BACKGROUND OF THE INVENTION

[0003] Others have described devices for the handling and/or removal of cerebrospinal fluid (CSF) to and from a patient.

[0004] For example, several patents disclose various methods for diverting or shunting CSF from the CSF space (ventricle, spinal column) to another portion of the body (*e.g.*, abdomen, peritoneal cavity). See, *e.g.*, 2,969,066; 3, 889, 687; 6,575,928 and 7,118,549. Others have described administering therapeutic agents to the CSF space, but do not disclose removing the CSF. See, *e.g.*, U.S. Patent Nos. 5,531,673; 6,056,725; 6,594,880; 6,682,508 and 6,689,756. Generally, the therapeutic agents are locally delivered to the brain but not to the greater cerebrospinal fluid space, which includes the brain and the spine. Others disclose removing CSF, but generally do not administer therapeutic agent or any other fluid. See, *e.g.*, U.S. Patent Nos. 3,889,687; 5,683,357; 5,405,316 and 7,252,659.

[0005] Devices exist having both input and output catheters for administering therapeutic agents or synthetic CSF and removing endogenous CSF, but the close spatial placement of the inflow and outflow catheters do not allow for flow of CSF throughout the cerebrospinal fluid space or full CSF exchange that provides access to the complete intracranial and

intraspinal CSF volume. *See, e.g.*, U.S. Patent Nos. 4,378,797; 4,904,237; 6,537,241 and 6,709,426.

[0006] Furthermore, publications disclosing the exchange of CSF describe replacing endogenous CSF with synthetic CSF replacement fluid. *See, e.g.*, U.S. Patent Publication No. 2003/0065309; and PCT Publication Nos. WO 01/154766 and WO 03/015710. In this way, the concentration of the toxic species may be diluted but not removed. It has been proposed to treat drug overdose or removal of tumor cells to clear debris before implantation of a ventriculo-peritoneal shunt system. Such an apparatus is unnatural in that it requires flushing the entire system with an artificially produced solution rather than removing the toxins of interest from the patient's endogenous CSF, requires liters of instilled replacement fluid to be delivered on a regular basis, is neither targeted nor focused for removal of specific toxins of interest and is only practical in an acute setting where liters of fluid could be instilled. *See, e.g.* PCT Publication No. WO 01/54766.

[0007] Various devices aimed at accessing the CSF or indirectly targeting the nervous system exist, however there exists no CSF purification system that allows for the direct, targeted, logical and disease-specific removal of one or more of target compounds or the use of a dual or multi-lumen catheter that influences or controls CSF flow, mixing and efficiency of turnover.

[0008] It is desirable to provide a method and system for processing and removal of one or more target compounds from the CSF of a patient. Recently, a treatment for Alzheimer's disease was suggested which relied on removal of CSF by diversion of the fluid from the brain (ventricular system) to another portion of the patient's body (e.g. abdomen/peritoneal cavity) using a modified ventriculo-peritoneal shunt system. *See, e.g.*, U.S. Patent Nos. 5,980,480 and 7,025,742. By continuously draining CSF at a low rate, the rationale was that the body's daily production of new CSF would dilute the concentration of contaminating substances remaining in the endogenous CSF. Such a system has several inherent limitations. The rate at which the concentration of toxic species is lowered is mediated by passive flow, is very slow, addresses only a fraction (milliliters) of the total CSF volume per hour, is not targeted or focused in removing specific items of interest and does not prevent reabsorption of toxic species back into the systemic circulation and thereby back into the CSF. *See, e.g.* U.S. Patent Nos. 5,980,480; 6,264,625; 6,689,085.

[0009] The present invention addresses this and other needs.

BRIEF SUMMARY OF THE INVENTION

[0010] The present invention provides systems and methods for conditioning cerebrospinal fluid (CSF).

[0011] Accordingly, in a first aspect, the invention provides methods for conditioning
5 cerebrospinal fluid (CSF) in a patient. In some embodiments, the methods comprise:

- a) removing CSF from a first location in a CSF space of the patient;
- b) conditioning the removed CSF; and
- c) returning the conditioned CSF to the patient at a second location in the CSF space;

wherein the removing and returning steps are performed concurrently during at least a portion
10 of a conditioning treatment.

[0012] In another aspect, the invention provides methods for conditioning cerebrospinal fluid (CSF) in a patient, the methods comprising:

a) introducing a catheter apparatus through a spinal (*e.g.*, sacral, lumbar, thoracic, cervical) access site into the spinal CSF space of a patient;

15 b) advancing the catheter apparatus through the spinal CSF space cranially (toward the brain) such that a distal port and a proximal port on the catheter apparatus are disposed within the CSF space and spaced-apart by a preselected distance;

c) withdrawing CSF through one of said ports;

d) conditioning the withdrawn CSF; and

20 e) returning the conditioned CSF through the other of said ports.

[0013] In another aspect, the invention provides methods for conditioning cerebrospinal fluid (CSF) in a patient, the methods comprising:

a) introducing a catheter apparatus into a brain ventricle or into the subarachnoid space of a patient;

25 b) advancing the catheter apparatus into the spinal CSF space such that a distal port and a proximal port on the catheter apparatus are disposed within the CSF space and spaced-apart by a preselected distance;

c) withdrawing CSF through one of said ports;

d) conditioning the withdrawn CSF; and

30 e) returning the conditioned CSF through the other of said ports.

[0014] In another aspect, the invention provides methods for conditioning cerebrospinal fluid in a patient, the methods comprising:

- a) introducing a catheter apparatus into a brain ventricle of a patient;
- b) adjusting spacing between a pair of ports on the catheter apparatus so one port lies
- 5 on one side of the ventricle and the other port lies on another side of the ventricle;
- c) withdrawing CSF through one of said ports;
- d) conditioning the withdrawn CSF; and
- e) returning the conditioned CSF to the ventricle through the other of said ports.

[0015] With respect to the embodiments of the methods, in some embodiments, the CSF is

10 removed or withdrawn and returned at substantially the same flow rate. In some embodiments, the CSF is removed or withdrawn and returned at the same flow rate. In some embodiments, the flow rate is in the range from about 0.04 ml/min to about 30 ml/min, for example, from about 5 ml/min to about 20 ml/min, for example, about 1, 2, 3, 5, 7, 10, 12, 15, 18 or 20 ml/min.

15 [0016] In some embodiments, the volume of CSF removed is below the volume that would induce a spinal headache or symptoms of overdrainage. In some embodiments, the volume of CSF removed from the patient never exceeds about 35-45 ml, for example, about 40 ml, 35 ml, 30 ml or 25 ml.

[0017] In some embodiments, the distance between the first location and the second

20 location is at least about 4 cm, for example, about 5, 10, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90 or 100 cm. In some embodiments, the distance between the first location and the second location is separated by at least about 2 vertebrae.

[0018] In some embodiments, the first location or the proximal port is at sacral S1 or lumbar L5 or above and the second location is at lumbar L3 or above. In some embodiments,

25 the first location or proximal port is at S1, L5, L4, L3, L2, L1 or above. In some embodiments, the second location or distal port is in the sacral, lumbar, thoracic or cervical CSF space. In some embodiments, the second location or distal port is in one or more ventricles. In some embodiments, the second location or distal port is in the cranial subarachnoid space.

30 [0019] In some embodiments, the first location or proximal port is in the cranial subarachnoid space. In some embodiments, the first location or proximal port is in one or more ventricles. In some embodiments, the second location or distal port is in the lumbar,

thoracic or cervical CSF space. In some embodiments, the second location or distal port is in the lumbar CSF space, for example at S1, L5, L4, L3, L2, L1 or above.

[0020] In some embodiments, the first location or proximal port and the second location or distal port is in the ventricular space. For example, both the first location or proximal port and the second location or distal port can on opposite sides of one ventricle. In another example, the first location or proximal port is in a first ventricle and the second location or distal port is in a second ventricle.

[0021] In some embodiments, the distance between the first location or proximal port and the second location or distal port is adjustable. For example, a pair of tubular members in a multilumen catheter can be axially adjusted relative to one another.

[0022] In some embodiments, the flow directions of removing or withdrawing and returning CSF are periodically reversed so that CSF is returned to the first location and removed from a second location during a portion of the treatment. For example, the flow reversal is a pulse to dislodge debris from removal or return ports.

[0023] In some embodiments, the methods further comprise the step of mixing the conditioned CSF with unconditioned CSF as the conditioned CSF is returned to the CSF space. In some embodiments, the methods comprise inducing a turbulent flow as the conditioned CSF is returned which enhances mixing. For example, the turbulent flow can be created by introducing a multilumen catheter comprising one or more helical flow paths, textured (*e.g.*, ribbed or bumped) flow paths, a T-separated flow path, bellows, balloons, fins, and/or multiple exit ports (*e.g.*, side holes or side vents). Turbulent flow can also be induced by high pressure injection (*i.e.*, “jetting”) or directed outflow.

[0024] In some embodiments, the conditioning comprises removing a targeted molecule (*e.g.*, protein, peptide, oligopeptide) from the CSF. For example, the conditioning can comprise one or more separation processes selected from the group consisting of biospecific affinity (*e.g.*, antibodies, nucleic acids, receptors, enzymes), immunoaffinity, cationic exchange, anionic exchange, hydrophobicity and various size exclusion thresholds.

[0025] In some embodiments, the methods further comprise the step of isolating the targeted molecule.

[0026] In some embodiments, the conditioning comprises removing pathological cells (*e.g.*, B-cell, T-cells, macrophages, erythrocytes and other blood cells) and cellular debris.

[0027] In some embodiments, the conditioning step is performed externally to the patient's body. In some embodiments, the conditioning step is performed using a conditioning unit implanted in the patient's body.

[0028] In some embodiments, the catheter apparatus consists essentially of a single catheter body having a lumen connected to the distal port and a separate lumen connected to the proximal port.

[0029] In some embodiments, the methods comprise ameliorating the symptoms of Alzheimer's Disease in a patient by removing at least one of beta-amyloid or tau proteins from CSF employing the methods and systems described above and herein.

[0030] In some embodiments, the methods comprise ameliorating the symptoms of Parkinson's Disease in a patient by removing at least one of alpha-synuclein proteins (including peptides or oligomers) from CSF employing the methods and systems described above and herein.

[0031] In some embodiments, the methods comprise ameliorating the symptoms of Amyotrophic Lateral Sclerosis (ALS) in a patient by removing at least one of insoluble superoxide dismutase-1 (SOD1), glutamate, neurofilament protein, and anti-GM1 ganglioside antibodies from CSF employing the methods and systems described above and herein.

[0032] In some embodiments, the methods comprise ameliorating the symptoms of cerebral vasospasm in a patient by removing at least one of blood cells (*e.g.*, erythrocytes), oxyhemoglobin and endothelin from CSF employing the methods and systems described above and herein.

[0033] In some embodiments, the methods comprise ameliorating the symptoms of encephalitis in a patient by removing at least one of the causative bacterial or viral entity, tumor necrosis factor-alpha (TNF α) and IgG from CSF employing the methods and systems described above and herein.

[0034] In some embodiments, the methods comprise ameliorating the symptoms of Guillain Barre Syndrome (GBS) in a patient by removing at least one of cells and inflammatory mediators including but not limited to C5a, TNF α , IL 2, IL-6, interferon- γ , IgG, and endotoxins from CSF employing the methods and systems described above and herein.

[0035] In some embodiments, the methods comprise ameliorating the symptoms of Multiple Sclerosis (MS) in a patient by removing at least one of T cells, B cells, anti-myelin antibodies and inflammatory mediators including but not limited to TNF α , IL 2, IL-6, interferon- γ from CSF employing the methods and systems described above and herein.

5 [0036] In some embodiments, the methods comprise ameliorating the symptoms of stroke in a patient by removing inflammatory mediators including but not limited to endothelin and enolase and cooling the CSF (and hence the CNS), employing the methods and systems described above and herein.

[0037] In a related aspect, the methods provide systems for conditioning cerebrospinal fluid (CSF) in a patient. In some embodiments, the systems comprise

i) a catheter assembly having a first lumen with a distal port and a second lumen with a proximal port, said catheter being adapted to be introduced in a CSF space and said ports being spaced axially apart;

15 ii) a pump connectable between the first and second lumens to induce a flow of CSF therebetween; and

iii) a conditioning component connectable between the first and second lumens to condition the CSF flowing therebetween.

[0038] With respect to the embodiments of the systems, in some embodiments, the catheter assembly consists essentially of a single tubular member having the first lumen and distal port and the second lumen and proximal port fixedly disposed therein.

[0039] In some embodiments, the catheter comprises a first tubular member having the first lumen and the distal port therein and a second tubular member having the second lumen and proximal port therein.

25 [0040] In some embodiments, the first and second tubes can be axially translated relative to each other to adjust the distance therebetween.

[0041] In some embodiments, the pump has a flow rate adjustable between about 0.04 ml/min to about 30 ml/min, for example, from about 5 ml/min to about 20 ml/min, for example, about 1, 2, 3, 5, 7, 10, 12, 15, 18 or 20 ml/min. In some embodiments, the pump comprises a peristaltic pump which is isolated from the CSF flow. In some embodiments, the pump is implantable(e.g., an Archimedes screw).

[0042] In some embodiments, the conditioning component is selected from the group consisting of biospecific affinity, immunoaffinity, cationic exchange, anionic exchange, hydrophobicity and size exclusion. For example, the conditioning component can be a column or a cartridge. In some embodiments, the catheter comprises the conditioning component (*e.g.*, bound to the inner surface of the catheter by covalent or non-covalent bonding).

[0043] With respect to size exclusion and filtration, the filtration component can be any type, *e.g.*, membranous, nanoparticulate, flat, tubular or capillary.

[0044] In some embodiments, the system has a CSF retention volume below about 40 ml, for example, below about 35, 30, 25 or 20 ml.

[0045] In some embodiments, the system is implantable. In some embodiments, the system is partially external.

DEFINITIONS

[0046] The term “patient” refers to any mammal. The mammal can be a non-human mammal, a non-human primate or a human. In some embodiments, the mammal is a domestic animal (*e.g.*, canine, feline, rodentia, etc.), an agricultural mammal (*e.g.*, bovine, ovine, equine, porcine) or a laboratory mammal (rodentia, rattus, murine, lagomorpha, hamster).

[0047] The term “CSF space” refers to any volume of cerebrospinal fluid found in the cranial or spinal areas that is in contact with any component of the nervous system, but not within the tissue. Interstitial fluid resides in the tissue.

[0048] The phrase “conditioning CSF” or “conditioned CSF” interchangeably refer to CSF wherein one or more target compounds have been partially, mostly or entirely removed.

[0049] The phrase “consisting essentially of” refers to the elements recited in the claim as well as insubstantial elements, and excludes elements that materially change the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0050] Figure 1 illustrates a sagittal cross-section through the brain and spinal cord and illustrates the location of the choroid plexus and the passive flow of CSF through the CNS.

The inset depicts the arachnoid granulations located along the major venous sinuses, which are the primary locations for CSF reabsorption.

[0051] Figure 2 provides a view of the ventricular system from the A) lateral surface, B) anterior surface, C) superior surface and D) detailed ventricular structure.

5 [0052] Figure 3 illustrates the ventricular anatomy of the brain in a 3 dimensional perspective.

[0053] Figure 4 depicts the Blood-Brain and Blood-CSF Barriers. A) fenestrated capillary allowing passage of water and solutes, B) brain capillaries with tight junctions between endothelial cells, forming blood-brain barrier; requires cellular transport, C) choroids plexus
10 epithelial cells form the blood-CSF barrier and allow water and solutes but require cellular transport, D) arachnoid villi allow one-way bulk flow of CSF into major venous sinuses.

[0054] Figure 5 illustrates the oligomeric hypothesis of neurodegenerative diseases. The multi-step process is thought to underlie a number of different neurologic conditions. The disease specific proteins undergo a specific biochemical modification which makes them
15 prone to join and form globular intermediates (known as oligomers). These oligomers are thought to be toxic and can continue to build on one another forming protofibrils and fibrils. The fibrils may then be isolated into an intracellular inclusion (e.g. tau tangles) or an extracellular deposit (e.g. A β plaque) in the case of Alzheimer's disease.

[0055] Figure 6A illustrates a schematic of the ventricular, spinal and ventriculo-spinal
20 approaches for accessing the CSF space for the efficient turnover of conditioned CSF. Figure 6B illustrates one embodiment of the dual- and single- ventricular approaches of the invention. Figure 6C illustrates one embodiment of the spinal approach of the invention.

[0056] Figure 7 illustrates a schematic of a single lumen system. A single-lumen system creates a local eddy (shading) with minimal mixing or access to cranial CSF.

25 [0057] Figure 8A illustrates a schematic of a dual lumen system of the invention. A multi-lumen system creates an active and dynamic flow with efficient mixing that is not limited by pressure volume as inflow and outflow are relatively equal. This allows for parallel processing of CSF with maximum turnover and provides access to the cranial and spinal space and entire CSF volume (mixing represented by shading). Figure 8B illustrates the
30 dramatic difference in CSF clearance produced with a multilumen system in which inflow and outflow are substantially apart (line D), adjacent (line C) compared to a single lumen

system (line B) compared to diffusion-limited flow (line A). Figure 8C illustrates the effect of catheter inflow/outflow distance on the rate of reprocessing of conditioned CSF.

[0058] Figure 9A and 9B illustrates cross-sections of sample dual or multilumen catheters, respectively, for use in the CSF space. These are but two examples of many embodiments that may be envisioned to achieve one of the ultimate goals of the invention which is a method to provide efficient mixing and turnover of CSF.

[0059] Figure 10 illustrates catheters with helical out flow paths which induce additional mixing at various outflow points. Figure 10A illustrates a single helical outflow path over last length (l) of catheter. A straight outflow lumen connects to the helical path. The catheter comprises a straight central inflow lumen. Figure 10B illustrates a dual helical outflow path catheter with central inflow path.

[0060] Figure 11A illustrates dual helical outflow paths exiting at different points along the catheter. The catheter comprises a single central inflow path. As described herein, the paths can be reversed, for example, by a pump mechanism. Therefore, a catheter with a single inflow path and multiple outflow paths could become a single outflow path with multiple inflow paths. Figure 11B illustrates how helical path directional changes as another means of creating a directed flow.

[0061] Figure 12A illustrates two catheters bound by a double collar. The collar is fixed to one catheter and slips on other such that the distance "d" between the two ends is adjustable. In this case, the inflow catheter is interfaced with the slipping portion of the collar. Figure 12B illustrates a dual lumen catheter that is encircled by a tight fitting thin walled cannula. The outflow lumen of the inner catheter has side ports such that, as the cannula is pulled back additional side ports or openings are exposed, thereby increasing the distance between the inflow and outflow.

[0062] Figure 13A illustrates a dual lumen catheter with addressable holes on one lumen. Figure 13B illustrates a two catheter system creating a dual lumen catheter. As shown, the outflow catheter is created by the space between the inner and outer catheters.

[0063] Figure 14A illustrates a dual lumen catheter with partially overlapping side ports for use in sub arachnoid to ventricular access. The holes surrounded by parenchyma would be sealed by the parenchyma. These would include the overlapping portion. Figure 14B

illustrates a close-up of an end showing one overlapping hole on the left. Figure 14C illustrates a middle section showing overlapping holes.

[0064] Figure 15A illustrates an end section. Figure 15B illustrates a catheter incorporating multiple balloons. The inflow and outflow lumens are seen on either side of the base “T-section.” The balloon inflation lumen is above the T-section. The three balloon inflation ports can be seen from the top through thin membranes which form the balloons. Figure 15C illustrates a cross-section of an end with inflow and balloon inflation lumens visible along with an inflation port.

[0065] Figure 16A-C illustrates balloons inflated. A catheter can contain single or multiple balloons. The balloons can be spherical or long. Long slender balloons are well-suited for a spinal column space. The distance between balloons can be uniform or of different lengths.

DETAILED DESCRIPTION

1. Introduction

[0066] The present invention provides methods, devices and systems for removing, detecting, returning and delivering compounds from and/or to a patient’s cerebrospinal fluid (CSF) space. The removal and/or delivery of specific compounds can be tailored to the pathology of the specific disease. The removal is targeted and specific, for example, through the use of specific size-exclusion thresholds, antibodies against specific toxins, and other chromatographic techniques, as well as delivery and/or removal of targeted therapeutic agents. The invention finds use as a diagnostic, therapeutic and drug delivery platform for a variety of diseases affecting the CNS by accessing the CSF space.

[0067] For the first time, the present invention offers a targeted, focused and logical treatment platform to treat a variety of debilitating and often devastating neurological diseases to which there are presently limited and ineffective treatment options. Exemplified disease conditions treatable by the present CSF processing systems and methods include, but are not limited to: Cerebral Vasospasm, Guillain Barre Syndrome, Alzheimer’s, Parkinson’s, Huntington’s, Multiple Sclerosis, Amyotrophic Lateral sclerosis, Spinal Cord Injury, Traumatic Brain Injury, Stroke, Cancer affecting the brain or spinal cord, Prion disease, Encephalitis from various causes, Meningitis from various causes, diseases secondary to

enzymatic or metabolic imbalances, Biological Warfare, etc. For the first time, the present invention offers patients a disease-modifying, disruptive technology that addresses the known disease pathogenesis and effectively ameliorates the symptoms of a number of neurologic conditions.

5 **[0068] CSF:** Cerebrospinal fluid (CSF) is primarily produced by the human CNS by vascular plexuses termed choroid plexus in the lateral third, and fourth, ventricles of the brain (Figure 1). This normally clear, watery fluid maintains a gradient between it and the interstitial fluid of the nervous system. Water and soluble substances are freely exchangeable between the CSF and the nervous system. Thus, many neurotransmitters, peptides and other
10 neuroactive substances can be found within the CSF. The functional role of many of these peptides is under current research. The concentration of various neuroactive substances in the CSF is of great interest, because it represents an indirect view that corresponds closely to the extracellular fluid in the immediate vicinity of the neurons in the brain and spinal cord. Thus, CSF serves two main functions: 1) by coating the brain and spinal cord it provides a
15 protective function, providing buoyancy and preventing traction on vessels and nerves upon impact to the skull or spinal column; 2) perhaps even more importantly, it contributes the maintenance of a constant composition of the neuronal environment. *See, Blumenfeld, H. (2002). "Neuroanatomy through Clinical Cases." 951.*

[0069] Neuroanatomy/Flow: In healthy adults, CSF is produced at a rate of about 0.3
20 ml/min, 18 ml/hour, or about 432 ml/day. However, the total volume found in the ventricles and subarachnoid space is about 150 ml (Figure 2). Thus, the total volume of CSF is turned over several (approximately three) times each day. The fluid produced in the lateral ventricles flows via the intraventricular foramen (of Monroe) into the third ventricle, then via the narrow cerebral aqueduct into the fourth ventricle (Figure 3). From there, it exits via the
25 midline posteriorly (foramen of Magendie) or laterally (foramen of Luschka) (Figure 2). The CSF then spreads over the entire surface of the brain and spinal cord, providing a constant balance of extracellular fluid to individual neurons throughout the CNS. The CSF is drained by small protrusions called arachnoid granulations, which are particularly prominent along the major venous drainage sites such as the superior sagittal sinus (Figure 1, inset). Fluid passes
30 from the subarachnoid space to the venous sinuses by a hydrostatic gradient. Some of the CSF is also drained via other routes, such as lymphatic vessels along cranial and spinal nerves. *See, Blumenfeld, H. (2002). "Neuroanatomy through Clinical Cases." 951.*

[0070] **Barriers:** In most organs, small-molecular weight substances pass the capillary wall with relative ease, and their concentration is therefore similar in the plasma as in the interstitial (extracellular) fluid. The composition of the interstitial fluid of the CNS differs from most other organs because of the selective properties of brain capillaries, known as the blood-brain barrier (BBB). This barrier is comprised of extensive tight junctions between endothelial cells, preventing the passage of a number of substances from the peripheral plasma (Figure 4). Similar to the BBB, the epithelium of the choroid plexus represents an additional barrier between blood and CSF, known as the blood-CSF barrier. Thus, many substances that can leave the capillaries of the choroid plexus cannot enter the CSF. Neurons depend on the precise control of ions and compounds in their extracellular environment for their normal functioning. *See*, Blumenfeld, H. (2002). "Neuroanatomy through Clinical Cases." 951.

[0071] **Neurologic Diseases:** Diseases affecting the nervous system are among the most devastating and debilitating medical conditions. Increasingly we understand the pathophysiology of a variety of endogenous and exogenous pathogens that can be found within the CSF that produce a direct or indirect deleterious effect on the CNS. This represents an opportunity for intervention and prevention or amelioration of the disease process. Furthermore, the system can be tailored to the individual disease process in a logical, targeted and focused manner.

[0072] The concept that numerous distinct disorders of the brain and spinal cord would require a different, disease-specific therapeutic intervention has been challenged by the discovery that several of the disorders have common underlying disease mechanisms. This provides an opportunity for intervention with a device platform that addresses a number of different diseases based on a few fundamental concepts involving the purification and modification of CSF based on size, biologic components and temperature.

[0073] It is now understood that a number of "endogenous pathogens" (neurotoxic molecules released from the brain into the CSF) and "exogenous pathogens" (cells and neurotoxic molecules from the peripheral circulation which enter the CSF) can perturb the normal environment of the CNS and are thought to play a key role in a number of diseases affecting the nervous system. *See*, Caughey, B. and P. T. Lansbury (2003). *Annu Rev Neurosci* 26: 267-98.

[0074] Many neurodegenerative disorders are characterized by aggregates of protein fibrils and neurotoxic oligomeric species and infiltrations of pathological inflammatory cell types (e.g., B-cells, T-cells, macrophages) that are implicated in progressive brain degeneration. See, Caughey, B. and P. T. Lansbury (2003). *Annu Rev Neurosci* 26: 267-98; and Taylor, J. P., J. Hardy, et al. (2002). *Science* 296(5575): 1991-5. See, Table 1 and Figure 5. Despite differences in the molecular composition of these protein fibrils as well as the brain regions and cell types affected in each disorder, these diseases share a similar pathological mechanism and therefore, they share similar mechanisms of treatment from a medical device point of view.

10 **TABLE 1**

Disorder	Current US Prevalence (persons)	Proteinacious Deposit	Abnormal Protein	Current Medical Treatment	Current US Cost/Year (billions)
Alzheimer's Disease (AD)	~ 4 million ~ 22 million by 2025	Senile plaques and neurofibrillary tangles	A β oligomers ; Tau oligomers	acetylcholinesterase inhibitors	\$100
Parkinson's Disease (PD)	~ 1 million	Lewy bodies	α -synuclein oligomers	L-dopamine	\$25
Multiple Sclerosis (MS)	~350,000	Demyelinating Plaques	Anti-myelin antibodies	interferon- β	\$10
Huntington's Disease (HD)	~30,000	Intraneuronal inclusions	Huntingtin oligomers	none	\$2.5
Amyotrophic Lateral Sclerosis (ALS)	~30,000	Intraneuronal inclusions	Insoluble SOD1	glutamate release inhibitors	\$1

[0075] **Immunotherapy:** Recently, the immunological concept in the treatment of conformational diseases has gained more attention and immunization approaches are being pursued in order to stimulate clearance, for example in Alzheimer's Disease (AD), of brain beta-amyloid protein (A β) plaques. They include both active and passive immunization techniques. Active immunization approaches employ various routes of administration, types

of adjuvants, the use of modified A β epitopes and/or immunogenic A β conjugates. *See*, Morgan, D., D. M. Diamond, et al. (2000). *Nature* 408(6815): 982-5. Passive immunization approaches include monoclonal antibodies or specific antibody fractions (Fabs) directed against specific A β epitopes. *See*, Monsonego, A. and H. L. Weiner (2003). *Science* 302(5646): 834-8. Plaque clearance as a result of immunotherapy may depend on multiple mechanisms. One theory involves direct interaction of antibodies, or Fab fragments, with the deposits resulting in disaggregation and microglial cell-mediated clearance. A second theory involves antibodies acting as a sink for A β peptide, removing it from the CNS and preventing plaque deposition in the brain by passive redistribution of soluble A β oligomers between brain, CSF, and plasma down a concentration gradient. *See*, Roberson, E. D. and L. Mucke (2006). *Science* 314(5800): 781-4. Significant data from animal studies exists to support both mechanisms with a substantially reduced A β burden in the transgenic mouse model along with improvement in memory disturbances. *See*, Janus, C., J. Pearson, et al. (2000). *Nature* 408(6815): 979-82. Promising evidence from A β immunization in transgenic mice showing clearance of A β plaques and improvement in cognitive disturbances, led to human clinical trials. Unfortunately, human patients actively immunized with an A β immunogen developed signs of meningoencephalitis as a consequence of active immunotherapy. *See*, Orgogozo, J. M., S. Gilman, et al. (2003). *Neurology* 61(1): 46-54; Bayer, A. J., R. Bullock, et al. (2005). *Neurology* 64(1): 94-101; and Gilman, S., M. Koller, et al. (2005). *Neurology* 64(9): 1553-62. Human patients passively immunized with antibodies against the A β protein developed neutralizing endogenous antibodies against the anti-A β antibodies, nullifying the therapeutic effect of the passive immunotherapy, and also potentially resulting in a detrimental increase in A β protein. *See*, Hock, C., U. Konietzko, et al. (2003). *Neuron* 38(4): 547-54; Nicoll, J. A., E. Barton, et al. (2006). *J Neuropathol Exp Neurol* 65(11): 1040-8; and Melnikova, I. (2007). *Nat Rev Drug Discov* 6(5): 341-2.

[0076] The primary concerns with both active and passive immunization lie in the pro-inflammatory consequences following immunization, which may lead to overactivation of microglia. In addition to the multiple inflammatory pathways thought to be involved in AD there are particular inflammatory pathways that are activated specifically following microglial stimulation, including release of proteases and cytokines, and activation of the oxidative burst that may exacerbate brain inflammation and AD-related neurodegeneration in the process of scavenging A β . In addition to inflammation, concerns exist for development of auto-antibodies with immune tolerance and the inability to reverse the treatment once

administered. Furthermore, for redistribution of soluble A β oligomers down the brain, CSF plasma concentration gradient, it is unknown whether A β is degraded in the plasma or taken up by specific organs. To address these concerns, one needs a therapy that prevents antibody from entering the CNS while still sequestering the toxic protein of interest.

5 [0077] The CSF Purification system described in the present invention serves as a broad platform technology for the treatment of a number of diseases affecting the nervous system. Several examples along with detailed rationale are provided below for a number of neurologic diseases to which there are presently limited or ineffective therapies.

10 [0078] It would be desirable to provide improved and alternative methods, systems, kits for the processing, purification and/or modification of CSF for a variety of purposes. The current invention possesses numerous benefits and advantages over previously described methods. First, the removal of agents based on size (such as red blood cells and their breakdown products in cerebral vasospasm, T- and B-cells in MS, auto-antibodies in GBS). With the recent advances in nanotechnology and ultrafiltration, it is now possible to remove agents on
15 the nanometer scale as opposed to micrometer, nearly a 1000x improvement in targeted filtration than previous systems. Prior filtration methods based on size were limited to 0.2 micron filters allowing the majority of smaller toxic molecules to pass directly through the filter and back to the patient.

20 [0079] Second, with the recent advances in immunotherapy, the current invention applies ex-vivo immunotherapy targeted at removal of pathogenic molecules from the CSF that directly affect the CNS. Antibodies provide an unprecedented level of specificity to molecules that are too small to remove by present-day size filters. In vivo immunotherapy applications have been met with a number of serious complications including encephalitis and death as described above. By securing the antibody to an immunoaffinity column, for
25 example using a streptavidin-biotin system (strongest chemical bond known), CSF is processed over the antibody cartridge and sequestration of toxic oligomers and/or proteins can be achieved with no risk of systemic antibody delivery, encephalitis or death. The use of biologic separation (including A β and Tau proteins in AD, alpha-synuclein in PD, etc.) can be beneficially applied to a number of diseases by altering the neuro-immune axis using a
30 platform ex-vivo immunotherapy approach.

[0080] Third, modulation of temperature by mild, moderate or severe hypothermia has been shown to have beneficial effects in terms of neuroprotection. Localized cooling of the CNS

without systemic effects on the heart, liver or kidney may provide an added advantage in a number of diseases including stroke, traumatic brain injury and spinal cord injury. Such objectives are met by the invention described hereinafter.

2. Systems of the Invention

5 [0081] The CSF purification system includes a multi-lumen catheter incorporating two or more lumens for the efficient exchange of CSF from either cranial and/or spinal CSF spaces. The present system creates a dynamic circulation with significant mixing within the cranial or spinal CSF space. The present invention allows for the processing of large volumes of CSF in a short amount of time while minimally impacting the endogenous intracranial/intraspinal
10 pressure and volume.

[0082] The purification (or compound removal) schema can be tailored to a specific disease or group of diseases based on a number of features, including size, affinity, biochemical properties and/or temperature, but more specifically purification schema based on diffusion, size-exclusion, ex-vivo immunotherapy using immobilized antibodies or antibody fragments,
15 hydrophobic/hydrophilic, anionic/cationic, high/low binding affinity, chelators, anti-bacterial, anti-viral, anti-DNA/RNA/amino acid, enzymatic, magnetic or nanoparticle-based systems. The system allows for passive flow but also includes a mechanism of active pumping with transient or continuous flow such that inflow and outflow are relatively equal to one another. Furthermore, a number of safety measures (including, but not limited to, pressure sensor,
20 velocity detector, bubble detector, pH, temperature, osmotic equilibrium, blood pressure, transmembrane pressure sensor) to ensure patient safety are included. Pressure sensors to continuously record/maintain/adjust intracranial and/or intraspinal pressures are also available. Programmable control of intake, output and overflow exhaust valves are additional contemplated features. The system is adjustable to a broad range of biologic parameters and
25 flows. Alarms and automatic on/off settings are further included to provide a signal for immediate attention and interrogation of the system. A given volume of CSF is outside the patient at any one time, less than that which produces symptoms associated with spinal headache or overdrainage.

[0083] Accordingly, the CSF purification/conditioning systems provide a dual/multi-lumen
30 catheter design. Flow studies have indicated that a dual or multilumen catheter with inflow and outflow separated from one another by an appropriate distance serves to create and maintain a dynamic circulation and efficient mixing/exchange of CSF. Given the normally

occurring variations in patient anatomy, such a distance may vary by individual. Therefore a system which allows for the variation in this distance *in situ* or prior to application (*i.e.*, implant) would provide a further improvement in performance for such systems in there application across the population. The flow dynamics created with such a system are

5 dramatically different than a single lumen system or a system where the inflow and outflow points are closely spatially located (Figure 7). Dye studies clearly demonstrate that the present system incorporating catheters with dual or multilumen designs and spaced apart inputs and outputs allow for a greater turnover of unprocessed CSF per minute, or more efficiency with minimum mixing of unprocessed and processed CSF, thereby accessing a

10 significantly larger portion of the entire CSF volume in a shorter period of time (Figure 8A). The present system design has dramatic effects on CSF physiology and flow. In the present dual lumen system, the distance of separation of inflow and outflow sites determines the maximum "column of CSF" that can be processed and cleared initially (Figure 8B). The catheter system with two or more lumens as well as multiple holes for inflow and outflow

15 along the length of the catheter not only minimizes clogging but provides greatly increased turnover and access to the basal cistern, ventricular, cranial as well as spinal subarachnoid CSF than previously described anywhere in the literature. The greater efficiency at removing compounds of interest arises from less reprocessing of the same fluid (Figure 8C).

[0084] Simple single lumen catheter systems produce only a local eddy, with minimal

20 mixing and therefore recirculation of much of the same, previously processed CSF. Such single lumen systems do not generate enough mixing to adequately draw or circulate fluid from the cranial CSF space that bathes the brain. *In vitro* studies indicate that the rate of mixing, the amount of new CSF turned over per minute as well as the access provided to turning over the cranial and spinal CSF volume multiple times using the present invention

25 results in a much more rapid, efficient and feasible CSF processing system that provides access to the entire CSF system than that attainable using a single lumen system. The present invention provides the ability to run parallel removal and return flows as opposed to sequential. Furthermore, the multilumen catheter can also incorporate an adjustable distance between the inflow and outflow areas, providing additional freedom for creating mixing and

30 circulation of CSF (Figure 12).

[0085] Parallel or continuous processing of removal and return flows using the multilumen systems of the invention provides several advantages over single lumen systems that require sequential processing. First, parallel processing is more efficient and requires fewer steps

than sequential processing. Multilumen systems that provide for continuous, parallel processing also can be conveniently automated and are more suitable for implantation. Because continuous, parallel processing systems can be designed to be closed, there is less need for human or manual intervention and better control of sterility. Moreover, continuous flow processing is not limited by the volume limitation on the amount processed; a wide range of flow rates and volume exchange can be accomplished (Figure 9). The only limitation is the dead space volume of the tubing, particularly in partially external systems.

[0086] The shape of the lumens is also a factor to consider. Studies have shown that simple circular lumens are more prone to clogging and necessitating repeated irrigation and/or catheter replacement. The dual/multi-lumen catheter systems described herein include a plurality of designs including, but not limited to, a combination of variable size and orientations of circular, oval, square, etc. designs to avoid catheter clogging. A combination of transient and/or continuous flow facilitates the maintenance of lumen patency and significantly decreases the risk of clogging associated with present day systems. The dual or multilumen system also allows for reversal of flow and rapid unclogging by intermittent reversal of flow by the pumping system. A dual lumen system provides the further advantage of allowing increased time periods in a particular flow direction by moving the clogging agents further away from the input.

[0087] The distal portion of the catheter can be constructed to promote maximal mixing and exchange of returned and unconditioned CSF upon return of the conditioned CSF. The elements that enhance mixing can be external or internal to a patient's body. One example is a helical or double helical design (*i.e.*, Figure 10, with or without bellows, to create maximum disruption/turbulence of passive CSF flow and more complete mixing and exchange of endogenous for processed CSF. Other examples include using jetting or directing outflow such that eddies or turbulence are created and thereby enhance mixing (Figure 11).

[0088] The catheter can contain a number of distal geometries to enhance mixing and exchange of CSF. One example is a T-catheter lumbar design (*i.e.*, Figures 13 and 15) in which both entry and exit lumens are inserted as a single catheter and the distal lumen either folds away or is deployed using a release mechanism such that one maximizes the distance between inflow and outflow sites and makes maximal surface area contact with the CSF space. Another example is the addition of small fins, a nonplanar surface, ribbed portions or a small balloon system (*i.e.*, Figures 15 and 16) anywhere along the length of a cranial or

spinal catheter that creates further mixing and exchange of endogenous and processed CSF. Examples of catheter designs that promote flow turbulence and mixing are shown in Figures 10-16.

[0089] A portion of the purification system can be incorporated into the catheter itself by fashioning it with a membrane that allows for the passive filtration of the endogenous CSF and/or equilibration with the processed CSF.

[0090] In some embodiments, the catheter includes radio-opaque markers for the accurate localization and confirmation of catheter tip location in the cranial or spinal CSF spaces. The radio-opaque markers can then be visualized using simple X-ray or computerized tomography. A variety of other methods can be utilized to confirm accurate catheter deployment and placement. This includes the use of an endoscope to directly visualize placement of the cranial or spinal catheter. This method may especially be useful in those patients with small cranial ventricles containing CSF or in those patients with spinal stenosis or scoliosis, where lumbar access is challenging.

[0091] One of the major concerns of any implanted device is the risk for infection. The risk of infection in the CSF is serious and includes meningitis, encephalitis and even death. A number of safety measures can be incorporated into the present invention to minimize and/or eliminate the possible risk of patient infection. First, the proximal end of the catheter can be tunneled a variable distance away from the entry site to minimize the risk of organisms tracking back in from the skin surface entry site. Second, meticulous care on a daily basis to clean the site of catheter access can be performed by a nurse or taught to the patient. Third, immediately before catheter placement as well as during the time the catheter remains indwelling during CSF processing and immediately after removal, antibiotics can be administered to the patient to further reduce the risk of infection. Fourth, the catheter system itself can be impregnated with a specific antibiotic of choice. Fifth, a specific metal that can produce a transiently charged surface, which has been shown to deter bacterial ingrowth and the incidence of catheter infections in general, can be incorporated. Sixth, an antibiotic of choice can be delivered into the CSF a certain time before, during or after CSF processing to further eliminate the risk of bacterial seeding or infection. Finally, an antibiotic cuff at one or more places along the catheter system can be placed to further reduce any risk of infection.

[0092] Another concern of any catheter system is the risk of kinking or physical obstruction. The current invention incorporates a number of safety sensors to ensure that

inflow and outflow are generally relatively equal. However, in addition, incorporating certain shape memory alloys in catheters (for example, in one of the lumens of Figure 9B) for use in the CSF space can be an added strategy of preventing kinking, maintaining shape, and allowing for maximum access of the CSF space. Nickel titanium is a shape memory alloy also commonly referred to as Nitinol. Above its transformation temperature, it is superelastic and able to withstand a large amount of deformation. Below its transformation temperature, it displays a shape memory effect. When it is deformed, it will remain in that shape until heated above its transformation temperature, at which time it will return to its original shape. Nitinol is typically composed of ~55% nickel by weight and making small changes in the composition can change the transition temperature of the alloy significantly which makes it suitable for many applications in medicine. In some embodiments, the catheter incorporates nickel titanium in its manufacturing. Such a catheter would allow for the easy entry of the catheter via the cranial or spinal access routes due to superelastic nature of Nitinol, while once in the CSF space the catheter would be return to its prior structure due to its shape memory. Nitinol's physical function resembles biological muscle; when activated it contracts. The contraction movement may be applied to any task requiring physical movement with low to moderate cycling speeds. The small size, light weight, ease of use and silent operation allow it to even replace small motors or solenoids. Such a catheter system that is internally adjustable and tailored to access varying areas of the cranial or spinal CSF space while minimizing the risk of kinking and catheter obstruction would be an additional feature in the present invention.

[0093] In some embodiments, the systems incorporate a conductive material or heat-exchange element into a portion of the catheter system (for example, in one of the lumens of Figure 9B) that would allow for the rapid and direct alteration of the CSF space for those disorders needing rapid adjustment of temperature. The neuroprotective effect of profound hypothermia has long been recognized, but use of hypothermia for the therapy of neuronal injuries was largely abandoned because of management problems and severe side effects, such as cardiac arrhythmia, shivering, infections, and coagulation disorders. In the past decade, it has come to be recognized that mild (34°C to 36°C), moderate (34°C to 28°C) and severe (<28°C) hypothermia allow for therapeutic modulation of temperature and may substantially avert brain damage caused by ischemia in both experimental stroke and other neuronal injuries. After focal cerebral ischemia, hypothermia reduced infarct volumes up to 90% and has been found to have significant beneficial effects on patients suffering from

traumatic brain injury or spinal cord injury. By contrast, hyperthermia has been shown to have a significantly negative effect on CNS histopathology and outcome.

[0094] Such a temperature adjustable cooling catheter designed specifically for the cranial or spinal CSF space, which can be used independently or in conjunction with an extracorporeal refrigerant system described in the prior literature, provides an added mechanism of rapid and direct CNS cooling without the systemic side effects seen on the heart or coagulation cascade seen when cooling the entire blood volume. Such a CSF cooling system has multiple utilities, including but not limited to, stroke, traumatic brain injury (TBI), spinal cord injury (SCI) and can be used separately or in conjunction with various purification/conditioning schema discussed above and herein. Temperature sensors of endogenous as well as processed CSF in addition to systemic body temperature can be incorporated into the heating/cooling system to appropriately record/maintain/adjust temperature.

[0095] The present systems allow for a number of different CSF inflow and outflow connections for the processing of CSF between any point in the CSF system such that total inflow and outflow are relatively equal. The spatial location of the inflow and outflow ports are sufficiently distant to allow for CSF flow throughout a major portion or the entire CSF space. The custom cranial or spinal catheters can be introduced via a number of routes, including but not limited to: single ventricular insertion, dual ventricular insertion, single level spinal insertion, dual/multi-level spinal insertion and ventriculo-spinal. In some embodiments, a first catheter is inserted into a brain ventricle or into the cervical spine, and a second catheter is inserted into the lumbar spine. In addition, any of the above systems could be fashioned to exchange CSF from any two points within the subarachnoid space. One example is a ventricular catheter with entry/exit sites communicating with the subarachnoid space overlying the adjacent brain parenchyma.

[0096] The present systems allow for the active movement of a large volume of CSF over time, and do not require the removal or diversion of CSF from the human body. Due to the varying entry and exit sites in the custom catheter, the system allows for the production of active, in addition to the normally passive, CSF flow. The active movement of CSF can be generated in a number of ways including but not limited to motorized pumps for active CSF withdrawal and return. Furthermore, the pump system can have a variety of mechanisms which facilitate the requirement that inflow and outflow are relatively equal. Examples of

suitable pumps include rotatory, syringe-driven, volumetric, peristaltic, piston, pneumatic, bellows, electromagnetic, magnetostrictive, hydraulic, and the like. The pumps can be a single apparatus with bi-directional functionality or two unidirectional pumps that are in communication with one another. There are several pumping mechanisms available to reach the desired endpoint of creating active, in addition to the normally passive, flow of CSF. The pump can be external or internal to the patient's body. Internal or implantable pumps are known in the art (*e.g.*, an Archimedes screw pump).

[0097] In some embodiments, the systems provide a customizable conditioning system based on the specific disease process being addressed. Removal of specific compounds can be targeted based on size-exclusion, specific antibodies, hydrophobic-hydrophilic interactions, anionic-cationic exchangers, compounds with high-low binding affinity, anti-bacterial, anti-viral, anti-DNA/RNA, immunotherapy-based, immuno-modulatory, enzymatic digestion, etc. In addition to the variety of neurochemical filtration approaches, other filtration systems based on electromechanical basis including radiofrequency, electromagnetic, acoustic wave, piezoelectric, electrostatic, atomic force and ultrasonic filtration can be employed. Other features can be added to the filter system including a differential centrifugal force to aid in the rapid separation of items of interest, *e.g.* ultrafiltrate, proteins, cells, etc.

[0098] In some embodiments, a cartridge-based schema can be employed for rapid changing or combinations of the aforementioned purification-based schema. For example, a system combining size, antibody and charge based approaches is envisioned with a single or multiple cartridges for the purification, such that when the time came for replacement of the purification filter, antibody, etc., it could be done in an easy to use, rapid exchange system. The conditioning system or chromatographic cartridges (*e.g.*, biospecific interaction, ionic exchangers, size exclusion) can be external or internal to a patient's body. In some embodiments, the conditioning cartridges or filters are contained within one or more lumens of the multilumen catheters. In some embodiments, the lumen of the catheters, or sections thereof, are coated (*e.g.*, by covalent or non-covalent binding) with chromatographic moieties (*e.g.*, biospecific capture moieties, including antibodies and nucleic acids, cationic or anionic exchangers, hydrophobic moieties, and the like).

[0099] In some embodiments, the systems include sensors for the intermittent or continuous monitoring and/or sampling of CSF levels of specific compounds or parameters of

interest. For instance, in cerebral vasospasm, one could serially sample and quantify levels of red blood cells, hemoglobin, endothelin, or other molecules and have an indication of how much the system has cleared the CSF. Similarly in Alzheimer's, one could measure levels of A β , Tau or other molecules and have an indication of production or removal of specific items of interest. Sensors may be utilized to record/maintain/adjust levels of specific compounds in the CSF noninvasively.

3. Methods of Use

a. Methods for Conditioning Cerebrospinal Fluid

[0100] The invention provides for methods for conditioning cerebrospinal fluid in a patient using the systems of the invention. The cranial or spinal catheters are placed using appropriate anatomic landmarks which are known to those skilled in the art such that said custom catheter is in contact with the CSF space of interest. The cranial catheter is placed at specific points and trajectory such that one enters the ventricular CSF space or cranial subarachnoid space overlying the brain parenchyma. In the case of a spinal catheter, a cannula is placed at any point along the spinal canal (often lumbar) and provides a conduit for which to place said custom spinal catheter into the CSF space. In particular, a multi-lumen spinal catheter can be inserted between a patient's lumbar vertebrae, for example, using a needle cannula to advance the catheter. In some embodiments, a sacral catheter is inserted in the sacral region above S1. In some embodiments, a lumbar catheter is inserted in the lumbar region above L5, L4, L3, L2 or L1. In other embodiments, a spinal catheter is inserted between thoracic or cervical vertebrae. For both spinal or cranial entry, the patient can be supine, sitting, or at any angle between 0° and 90°.

[0101] CSF is removed from the cranial or spinal CSF space passed through a disease-specific conditioning system and returned to a different location in the cranial or spinal CSF space. CSF is removed using a combination of natural passive flow but augmenting it with a pumping mechanism to produce an active CSF flow dynamics. The volume of CSF outside the body at any given time is less than that which would produce a spinal headache or symptoms of overdrainage (about 40 ml). The locations of the catheter may vary but include single, multi-lumen or a combination of catheters placed via single ventricular insertion, dual ventricular insertion, single level spinal insertion, dual/multi-level spinal insertion and ventriculo-spinal.

[0102] One exemplification includes use of a single level spinal insertion that is inserted in the lumbar space and fed cranially such that the catheter tip is in the cervical region. In this example, CSF inflow may be from the cervical portion and output from the lumbar portion and/or anywhere along the length of the multi-lumen catheter, depending on the number and location of exit ports along the outflow lumen. In another embodiment, inflow can be at the lumbar region and outflow at the cervical, subarachnoid or ventricular regions. In another embodiment, both the inflow and outflow ports are in the ventricular space, for example, with one port in a first ventricle and a second port in a second ventricle. In another embodiment, the inflow and outflow ports are located at different sides of the same ventricle.

[0103] The flow rates may be varied and are limited by the pressure differential placed on the catheter walls, but generally can be in the range of 0.04 ml/min to 30 ml/min, for example, about 5 to 20 ml/min, for example, about 0.5, 1, 2, 5, 8, 10, 12, 15, 20 ml/min.

[0104] The CSF is then conditioned using a variety of mechanisms as described above and generally include size, biospecific and/or temperature-mediated mechanisms. In performing the conditioning step, the removed or withdrawn CSF is contacted with one or more substrates comprising chromatographic, electrochemical or electromechanical selection agents.

[0105] The methods provide a customizable conditioning schema based on the specific disease process being addressed and the target compounds to be removed from the CSF.

Depending on the one or more target compounds to be removed (*e.g.*, proteins, oligomeric peptides, amino acids, nucleic acids, bacteria, etc.), the CSF can be contacted with one or more substrates comprising size-exclusion filtration, hydrophobic-hydrophilic interactions, anionic-cationic exchangers, compounds with high-low binding affinity, anti-bacterial, anti-viral, biospecific interactions including nucleic acid hybridization and immunoaffinity (*e.g.*, antibodies or non-antibody binding proteins), enzymatic digestion, or a combination thereof. Antibodies can be whole immunoglobulin molecules or fragments thereof (*e.g.*, FAb, single chain variable regions (scFv), variable regions). Non-antibody binding molecules, for example, based on A-domain scaffolding, also find use. In addition to the variety of chromatographic approaches, filtration systems based on electromechanical bases also find use, including radiofrequency, electromagnetic, acoustic wave, piezoelectric, electrostatic, atomic force and ultrasonic filtration can be employed. The CSF may also be subject to

differential centrifugal force to aid in the rapid separation of items of interest, e.g. ultrafiltrate, proteins, cells, etc.

[0106] In some embodiments, the CSF is contacted with multiple substrates, e.g., combining size, biospecific and charge-based selection criteria. The conditioning step can be performed external or internal to a patient's body. In some embodiments, the conditioning substrates are contained within one or more lumens of the multilumen catheters. In some embodiments, the lumen of the catheters, or sections thereof, is coated (e.g., by covalent or non-covalent binding) with chromatographic moieties (e.g., biospecific capture moieties, including antibodies and nucleic acids, cationic or anionic exchangers, hydrophobic moieties, and the like).

[0107] The concept of ex-vivo immunotherapy (i.e., immunoaffinity) using the CSF is itself a broadly applicable and novel component of the present invention. A number of conditions affecting the nervous system are now better understood and a common feature is a disruption in the neuroimmune axis or weak points in the blood brain barrier allowing B-cells, T-cells and the humoral and cell-mediated immune responses. In both instances, the normal neuronal architecture is victim to a broad range of neuro-inflammatory components and reactive oxidative stress proteins. The present invention allows for targeted removal of inflammatory cells and proteins and elimination and/or neutralization of oxidative stress proteins.

[0108] With regards to immunotherapy, present day active and passive immunotherapy treatments carry significant risk of encephalitis or generalized neuronal inflammation. By harnessing the immunotherapy components in an immobilized immunoaffinity approach, one can bring the CSF to the antibody and prevent any risk of mounting a generalized immune response against oneself. Furthermore, this eliminates the risk of autoantibodies against systemically delivered immunotherapies, which could have devastating effects and high mortality in a subset of patients. Cartridge-based schema would allow for further rapid replacement of the conditioning approach.

[0109] The methods contemplate the periodic re-use or re-charging of the filtration/processing component of the system. For instance, in the ex-vivo immunotherapy approach, a specific eluent can be used to release the captured oligomers or proteins and regenerate the active antigen binding sites on the antibodies. Furthermore, this eluted compound represents a purified human protein which can then be used as a

“neuropharmaceutical” agent. For example, in Alzheimer’s disease, purified A β or Tau components may then be released and used for a variety of other commercial or research studies involving the structure-function activity of disease-specific compounds in human disease. Also, the ability to automatically or periodically collect CSF or specific

5 subcomponents and store/freeze creating a CSF bank for specific disease processes is contemplated.

[0110] The conditioned endogenous CSF is then returned back to a CSF space in a different location than from which it was drawn. The second location or distal port for outflow or output is at a sufficiently different location from the first location or proximal port for inflow or input to create mixing of the conditioned and unconditioned CSF through a majority of the CSF space. For example at least about 50%, 60%, 70%, 80%, 90% of the conditioned and unconditioned CSF in the CSF space can be mixed. The inflow and outflow ports usually can be at least two vertebrae apart, for example, if both ports are in the spinal area. In other embodiments, one of the inflow or outflow ports can be in the spine (*e.g.*, sacral, lumbar, thoracic or cervical) and the other inflow or outflow port can be in the subarachnoid or ventricular space. In some embodiments, both the inflow and outflow ports are in the ventricular space, for example, where the inflow port is in a first ventricle and the outflow port is in a second ventricle (dual-ventricular embodiment). Depending on the design of the system, the quantitative distance between the inflow and outflow ports can be at least about 4 cm, for example, at least about 5 cm, 8 cm, 10 cm, 12 cm, 15 cm, 20 cm, 30 cm, 40 cm, 50 cm, or 60 cm, or longer, depending on the length of spine of an individual patient.

[0111] As discussed above and herein, one or more different geometries in the distal portion of the outflow lumen of the catheter facilitate turbulence mixing upon return of the conditioned CSF. For example, the distal portion of the outflow lumen can be configured to be a single or double helical conformation, contain multiple exit ports (*i.e.*, side holes or vents), have textures surfaces that induce turbulence (*e.g.*, bumps, ribbing, etc.), have balloons, bellows, fins or turbines. A T-catheter configuration also finds use. The flow rate can also be increased in the distal portion of the outflow lumen, *e.g.*, by high pressure injection or jetting.

[0112] The removal or withdrawing steps and the return steps can be performed concurrently, for parallel processing. This allows for a closed system and continuous processing or conditioning of the CSF, the advantages of which are described herein.

Overall, the inflow and outflow rates can be equal or substantially equal. Active flow can be maintained using a pump, as discussed above for the systems. The active flow rate can be uniform or discontinuous, as needed. Also, the flow path direction of the CSF can be reversed, periodically, intermittently, or throughout the duration of a treatment, such that the inflow port becomes the outflow port and the outflow port becomes the inflow port.

[0113] In addition to removal of specific toxins from the CSF, the present methods contemplate the delivery of therapeutic agents on the return cycle. That is, after a given volume is passed through the specific purification schema of interest, a specific pharmacologic agent or drug can be administered directly to the CNS and bypass the blood brain barrier. This provides the opportunity for specific delivery of pharmaceuticals to the CNS without the often many systemic side effects associated with oral or intravenous delivery. One of the challenges of drug delivery via the CSF is designing the drug to penetrate the brain/spinal cord parenchyma. A variety of ways including adjusting the hydrophilicity or using liposome-based approaches in conjunction with the system described herein may be envisioned. Thus, for the first time, the system described herein allows for the combined removal of specific toxins as well as delivery of specific therapeutic agents to the CNS.

[0114] The present methods also contemplate the infusion of artificial CSF fluid into the system, if needed, at any time. The combined purification of CSF with return of artificial CSF with appropriate physical/chemical safeguards in addition to the purified CSF is but one possibility. The system may also be primed with such a physiologically compatible artificial CSF solution.

b. Methods of Ameliorating Disease Conditions

i. Alzheimer's Disease (AD)

[0115] Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by abnormal accumulations of amyloid plaques and neurofibrillary tangles. Amyloid plaque formation is thought to be partly due to failure of clearance of beta-amyloid protein (A β). APP (amyloid precursor protein) generates various forms of amyloid A β through enzymatic processing. See, Blennow, K., M. J. de Leon, et al. (2006). *Lancet* 368(9533): 387-403. Diffusible oligomers of A β (from plaques) inhibit long term potentiation, cause membrane damage, alter membrane fluidity, and act as pore-forming toxins. See, Caughey, B. and P. T. Lansbury (2003). *Annu Rev Neurosci* 26: 267-98; and Glabe, C. G. (2006). *Neurobiol Aging*

27(4): 570-5. In AD, tau proteins also aggregate, resulting in degeneration of neuronal axons and dendrites and producing neurofibrillary tangles. Tau protein accumulation leads to cellular oxidative stress, which may be a causal factor in tau-induced neurodegeneration.

See, Dias-Santagata, D., T. A. Fulga, et al. (2007). *J Clin Invest* 117(1): 236-45. Specifically,

5 highly reactive oxygen species oxidize lipids, proteins, and DNA, leading to tissue damage and cell death. These markers for oxidized lipids and proteins accumulate in regions that are particularly affected in neurodegenerative diseases. Markers of oxidative damage have been detected in brain tissue from patients with AD and other neurodegenerative disorders. See, Koo, E. H., P. T. Lansbury, Jr., et al. (1999). *Proc Natl Acad Sci U S A* 96(18): 9989-90.

10 Free radical injury also appears to be a fundamental pathophysiologic mediator of tissue injury in human disease, including acute ischemic stroke, amyotrophic lateral sclerosis, Parkinson's disease, and AD. See, Taylor, J. P., J. Hardy, et al. (2002). *Science* 296(5575): 1991-5. Current therapies for AD are only marginally effective, as they may not slow rate of neurodegeneration, and have significant side-effects and some (immunization strategies) are
15 tentative at best.

[0116] In contrast, CSF processing of amyloid and tau proteins and neutralization of reactive oxidative species among others is both a symptomatic and disease-modifying treatment through its ability to reduce, limit, and prevent plaque and tangle formation as well as counteract neuroinflammation. It has the ability to address the disease process from
20 multiple different perspectives based on our present day understanding of disease pathogenesis. It may also be safer due to lower risk of liver damage and brain inflammation compared to current pharmacologic and immunotherapeutic regimens, respectively.

[0117] Accordingly, the present methods provide for ameliorating or reducing the symptoms of Alzheimer's disease by reducing or eliminating the presence of beta-amyloid and/or tau proteins in the CSF using the systems described herein. The methods comprise
25 removing CSF from a patient, as described herein; removing at least one of pathological proteins, including A β and tau, and inflammatory mediators (*e.g.*, cytokines, including TNF- α , IL-1, IL-2, IL-6, IL-12, interferon- γ , etc.) from the CSF, and returning the endogenous CSF to the patient, wherein the removing and returning steps are performed
30 concurrently during at least a portion of the treatment. In some embodiments, the A β or tau proteins and/or inflammatory mediators are removed from the CSF using an immunoaffinity column or a size exclusion column, or both.

[0118] In another embodiment, the methods provide for ameliorating or reducing the symptoms of Alzheimer's disease by introducing a catheter apparatus through a spinal access site into a spinal CSF space of a patient; advancing the catheter apparatus through the spinal CSF space cranially toward the brain so that a distal port and a proximal port on the catheter apparatus are disposed within the CSF space and spaced-apart by a preselected distance or adjusted to an appropriate distance; withdrawing CSF through one of said ports; removing at least one of A β or tau proteins or inflammatory mediators from the withdrawn CSF thereby conditioning the CSF; and returning the conditioned CSF through the other of said ports.

[0119] Further embodiments for treating Alzheimer's disease are as discussed above and herein.

ii. Parkinson's Disease (PD)

[0120] Parkinson's disease (PD) is caused by a loss of dopamine-containing pigmented neurons in the substantia nigra. Free radical injury and formation of alpha-synuclein fibrils and oligomers (i.e., peptides) are involved in pathogenesis of PD. *See*, Steece-Collier, K., E. Maries, et al. (2002). *Proc Natl Acad Sci U S A* 99(22): 13972-4. Current treatments (dopamine replacement therapy with L-dopa, Catechol-O-methyl transferase (COMT) inhibitors, amantadine and anticholinergic medications for symptomatic relief, surgery with deep brain stimulation) do not have a long-lasting effect, do not address the cause of disease and can have debilitation side-effects including dyskinesias. *See*, Dunnett, S. B. and A. Bjorklund (1999). *Nature* 399(6738 Suppl): A32-9; Dawson, T. M. and V. L. Dawson (2003). *Science* 302(5646): 819-22; and DeKosky, S. T. and K. Marek (2003). *Science* 302(5646): 830-4. There is a need for treatment that halts degeneration by removing free radicals and neurotoxic species. *See*, Shoulson, I. (1998). *Science* 282(5391): 1072-4. CSF filtration has fulfills that unmet medical need and can represent a disease-modifying mechanism for new PD treatments.

[0121] Accordingly, the present methods provide for ameliorating or reducing the symptoms of Parkinson's disease by reducing or eliminating the presence of alpha-synuclein fibrils and/or oligomers in the CSF using the systems described herein. The methods comprise removing CSF from a patient, as described herein; removing at least one of alpha-synuclein proteins and inflammatory mediators from the CSF, and returning the endogenous CSF to the patient, wherein the removing and returning steps are performed concurrently during at least a portion of the treatment. In some embodiments, the alpha-synuclein fibrils

and oligomers are removed from the CSF using an immunoaffinity column or a size exclusion column, or both.

[0122] In another embodiment, the methods provide for ameliorating or reducing the symptoms of Parkinson's disease by introducing a catheter apparatus through a spinal access site into a spinal CSF space of a patient; advancing the catheter apparatus through the CSF space cranially toward the brain such that a distal port and a proximal port on the catheter apparatus are disposed within the CSF space and spaced-apart by a preselected distance or adjusted to an appropriate distance; withdrawing CSF through one of said ports; removing at least one of alpha-synuclein proteins and inflammatory mediators from the withdrawn CSF thereby conditioning the CSF; and returning the conditioned CSF through the other of said ports.

[0123] Further embodiments for treating Parkinson's disease are as discussed above and herein.

iii. Amyotrophic Lateral Sclerosis (ALS)

[0124] Amyotrophic lateral sclerosis (ALS)/Lou Gehrig's Disease is a rapidly progressive, invariably fatal motor neuron disease that attacks the nerve cells responsible for controlling voluntary muscles. *See*, Rowland, L. P. (1995). *Proc Natl Acad Sci U S A* 92(5): 1251-3. Both the upper motor neurons and the lower motor neurons degenerate or die, ceasing to send messages to muscles. ALS patients had higher levels of glutamate in the serum and spinal fluid. Laboratory studies have demonstrated that neurons begin to die off when they are exposed over long periods to excessive amounts of glutamate. *See*, Rowland, L. P. (1995). *Proc Natl Acad Sci U S A* 92(5): 1251-3. Increased levels of neurofilament protein were found in CSF of ALS patients as well as increased levels of antibodies against GM1-gangliosides, AGM1-gangliosides and sulfatides in 20%, 15%, 8% of CSF of ALS patients, respectively. *See*, Valentine, J. S. and P. J. Hart (2003). *Proc Natl Acad Sci U S A* 100(7): 3617-22; and Banci, L., I. Bertini, et al. (2007). *Proc Natl Acad Sci U S A* 104(27): 11263-7. Thus, antibodies may be implicated in ALS by impairing the function of motor neurons, interfering with the transmission of signals between the brain and muscle. Free radical injury is also likely to be involved in ALS. A marker of oxidative stress and lipid peroxidation, 4-hydroxynonenal (HNE), was elevated in the CSF of patients with sporadic ALS. Current clinical treatments for ALS (Riluzole) that reduce the amount of glutamate released do not reverse the damage already done to motor neurons and cause side-effects such as

hepatotoxicity. In ALS, CSF purification would reduce excessively high glutamate levels in CSF and reduce oxidative species, thus prolonging the lifespan of motor neurons w/o serious side effects such as liver damage, and it would remove autoimmune antibodies and reactive oxidative species from CSF.

5 [0125] Accordingly, the present methods provide for ameliorating or reducing the symptoms of Amyotrophic lateral sclerosis (ALS) by reducing or eliminating the presence of one or more of insoluble superoxide dismutase-1 (SOD1), glutamate, neurofilament protein, and anti-GM1 ganglioside antibodies in the CSF using the systems described herein. The methods comprise removing CSF from a patient, as described herein; removing at least one
10 of insoluble superoxide dismutase-1 (SOD1), glutamate, neurofilament protein, and anti-GM1 ganglioside antibodies or other inflammatory mediators from the CSF, and returning the endogenous CSF to the patient, wherein the removing and returning steps are performed concurrently during at least a portion of the treatment. In some embodiments, the insoluble superoxide dismutase-1 (SOD1), glutamate, neurofilament protein, anti-GM1 ganglioside
15 antibodies or other inflammatory mediators are removed from the CSF using one or more of an immunoaffinity column, a size exclusion column, an anionic exchange column, a cationic exchange column, and a Protein A or Protein G column.

[0126] In another embodiment, the methods provide for ameliorating or reducing the symptoms of Amyotrophic lateral sclerosis (ALS) by introducing a catheter apparatus
20 through a spinal access site into a spinal CSF space of a patient; advancing the catheter apparatus through the spinal CSF space toward the brain so that a distal port and a proximal port on the catheter apparatus are disposed within the CSF space and spaced-apart by a preselected distance or adjusted to an appropriate distance; withdrawing CSF through one of said ports; removing at least one of insoluble superoxide dismutase-1 (SOD1), glutamate,
25 neurofilament protein, anti-GM1 ganglioside antibodies or other inflammatory mediators from the withdrawn CSF thereby conditioning the CSF; and returning the conditioned CSF through the other of said ports.

[0127] Further embodiments for treating Amyotrophic lateral sclerosis (ALS) are as discussed above and herein.

30 iv. Cerebral Vasospasm

[0128] Cerebral vasospasm is a time-dependent narrowing of cerebral vessel caliber, likely due to blood in the subarachnoid space (post cerebral aneurysm rupture, subarachnoid

hemorrhage (SAH), craniocerebral trauma, bacterial meningitis, after surgery in the sellar/parasellar region, etc.). *See, Macdonald, R. L., R. M. Pluta, et al. (2007). Nat Clin Pract Neurol 3(5): 256-63.* Hemolysis is necessary for vasospasm to develop and oxyhemoglobin is believed to be one of the many vasoactive substance released. Elevated levels of oxyhemoglobin are maintained in the CSF over the duration of vasospasm. In contrast, most other vasoactive agents released after clot lysis are rapidly cleared from the CSF. *See, Macdonald, R. L., R. M. Pluta, et al. (2007). Nat Clin Pract Neurol 3(5): 256-63.* In subarachnoid patients with vasospasm, endothelin in the CSF remained at or increased above levels measured before surgery. The increase coincided with the appearance of vasospasm as documented by transcranial doppler and clinical symptoms. In SAH patients who did not develop vasospasm, the concentration of endothelin in the CSF decreased with time. *See, Macdonald, R. L., R. M. Pluta, et al. (2007). Nat Clin Pract Neurol 3(5): 256-63.* Current therapies (calcium channel blockers, hypervolemic, hypertensive therapy and hemodilution (HHH therapy)) are not effective in preventing vasospasm. CSF filtration is more likely to be therapeutic by early and direct removal of blood clot, red blood cells, platelets and the downstream cascades involving oxyhemoglobin and endothelin that lead to vasospasm.

[0129] Accordingly, the present methods provide for ameliorating or reducing the symptoms of cerebral vasospasm by reducing or eliminating the presence of one or more of blood cells (*e.g.*, erythrocytes), hemoglobin, oxyhemoglobin, endothelin or other inflammatory mediators in the CSF using the systems described herein. The methods comprise removing CSF from a patient, as described herein; removing at least one of blood cells, hemoglobin, oxyhemoglobin, endothelin or inflammatory mediators from the CSF, and returning the endogenous CSF to the patient, wherein the removing and returning steps are performed concurrently during at least a portion of the treatment. In some embodiments, the oxyhemoglobin and endothelin are removed from the CSF using one or more of an immunoaffinity column, a size exclusion column, an anionic exchange column, and a cationic exchange column.

[0130] In another embodiment, the methods provide for ameliorating or reducing the symptoms of cerebral vasospasm by introducing a catheter apparatus through a spinal access site into a spinal CSF space of a patient; advancing the catheter apparatus through the spinal CSF space toward the brain so that a distal port and a proximal port on the catheter apparatus are disposed within the CSF space and spaced-apart by a preselected distance or adjusted to

an appropriate distance; withdrawing CSF through one of said ports; removing at least one of blood cells, hemoglobin, oxyhemoglobin, endothelin or inflammatory mediators from the withdrawn CSF thereby conditioning the CSF; and returning the conditioned CSF through the other of said ports.

- 5 [0131] Further embodiments for treating cerebral vasospasm are as discussed above and herein.

v. Encephalitis

[0132] Encephalitis is inflammation of the brain due to multiple causes: HSV (herpes simplex virus), Lyme disease, syphilis, bacterial infection, etc. Infants younger than 1 year and adults older than 55 are at greatest risk of death from encephalitis. *See*, Vernino, S., M. Geschwind, et al. (2007). *Neurologist* 13(3): 140-7. Current therapies (corticosteroids to reduce brain swelling and NSAIDs to decrease fever) do not target the cause of encephalitis. Levels of sTNF-R (reflects biologic activity of TNF-alpha, a major inflammatory mediator) were significantly higher in the CSF and serum of children with acute encephalitis than in those of control subjects. *See*, Vernino, S., M. Geschwind, et al. (2007). *Neurologist* 13(3): 140-7. Levels of IgG were increased in herpes simplex encephalitis. *See*, Vernino, S., M. Geschwind, et al. (2007). *Neurologist* 13(3): 140-7. CSF processing could restore levels of TNF-alpha and IgG to physiologic levels, reduce inflammation and aid in removal of viruses, parasites, prions, fungi and bacteria. Further applications include treating victims of biologic warfare (anthrax, botulinum, ricin, saxitoxin, etc.) by directly removing the toxin of interest from attacking the CNS.

[0133] Accordingly, the present methods provide for ameliorating or reducing the symptoms of encephalitis by reducing or eliminating the presence of one or more of tumor necrosis factor-alpha (TNF α) and IgG in the CSF using the systems described herein. The methods comprise removing CSF from a patient, as described herein; removing at least one of TNF α and IgG or other inflammatory mediators from the CSF, and returning the endogenous CSF to the patient, wherein the removing and returning steps are performed concurrently during at least a portion of the treatment. In some embodiments, the TNF α and IgG are removed from the CSF using one or more of an immunoaffinity column, a size exclusion column, an anionic exchange column, a cationic exchange column and a Protein A or Protein G column.

[0134] In another embodiment, the methods provide for ameliorating or reducing the symptoms of encephalitis by introducing a catheter apparatus through a spinal access site into a spinal CSF space of a patient; advancing the catheter apparatus through the spinal CSF space toward the brain so that a distal port and a proximal port on the catheter apparatus are disposed within the CSF space and spaced-apart by a preselected distance or adjusted to an appropriate distance; withdrawing CSF through one of said ports; removing at least one of TNF α and IgG or other inflammatory mediators from the withdrawn CSF thereby conditioning the CSF; and returning the conditioned CSF through the other of said ports.

[0135] Further embodiments for treating encephalitis are as discussed above and herein.

vi. Guillain Barre Syndrome (GBS)

[0136] Guillain Barre Syndrome (GBS) is divided into the two major subtypes: acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN). See, Parkhill, J., B. W. Wren, et al. (2000). *Nature* 403(6770): 665-8; and Yuki, N., K. Susuki, et al. (2004). *Proc Natl Acad Sci U S A* 101(31): 11404-9. In Europe and North America, GBS is usually caused by AIDP with prominent lymphocytic infiltration of the peripheral nerves and macrophage invasion of myelin sheath and Schwann cells. Activated complement found in cerebrospinal fluid of Gullain-Barre and multiple sclerosis (MS) patients may contribute to demyelination. See, Parkhill, J., B. W. Wren, et al. (2000). *Nature* 403(6770): 665-8; and Yuki, N., K. Susuki, et al. (2004). *Proc Natl Acad Sci U S A* 101(31): 11404-9. Treatment of GBS is subdivided into symptomatic management of severely paralyzed patients requiring intensive care and ventilatory support, and specific disease therapy to lessen the nerve damage. Immunomodulating treatments such as plasmapheresis and intravenous immunoglobulin are indicated for patients who are unable to walk independently. Results of international randomized trials have shown equivalent efficacy of both plasmapheresis and intravenous immunoglobulin, but corticosteroids are not effective. See, McKhann, G. M., J. W. Griffin, et al. (1988). *Ann Neurol* 23(4): 347-53; and Kuwabara, S., M. Mori, et al. (2001). *Muscle Nerve* 24(1): 54-8. Repeated filtration of CSF may remove pathogenetically relevant cells, immunoglobulins and polypeptides. Observations in 12 severe Guillain-Barre patients treated with CSF filtration indicate that it is a safe and effective procedure. CSF filtration and plasma exchange therapies were at least equally efficacious, and a patient with severe disease who did not respond to plasma exchange recovered completely with CSF filtration. See, Wollinsky, K. H., P. J. Hulser, et al.

(2001). *Neurology* 57(5): 774-80. CSF filtration (in vitro testing) effectively removed cells and inflammatory mediators (e.g. C5a, TNF- α , IL-2, IL-6, interferon- γ , IgG, endotoxins, and cells). See, Wollinsky, K. H., P. J. Hulser, et al. (2001). *Neurology* 57(5): 774-80. Thus, studies show that CSF filtration is at least as effective as plasmapheresis and it reduces, limits, and prevents nerve damage by removing lymphocytes, macrophages, complement proteins and other inflammatory agents.

[0137] Accordingly, the present methods provide for ameliorating or reducing the symptoms of Guillain Barre Syndrome (GBS) by reducing or eliminating the presence of one or more of cells and inflammatory mediators selected from the group consisting of C5a, TNF- α , IL-2, IL-6, interferon- γ , IgG, and endotoxins in the CSF using the systems described herein. The methods comprise removing CSF from a patient, as described herein; removing at least one of cells and inflammatory mediators selected from the group consisting of C5a, TNF- α , IL-2, IL-6, interferon- γ , IgG, and endotoxins from the CSF, and returning the endogenous CSF to the patient, wherein the removing and returning steps are performed concurrently during at least a portion of the treatment. In some embodiments, the cells and inflammatory mediators selected from the group consisting of C5a, TNF- α , IL-2, IL-6, interferon- γ , IgG, and endotoxins are removed from the CSF using one or more of an immunoaffinity column, a size exclusion column, an anionic exchange column, a cationic exchange column and a Protein A or Protein G column.

[0138] In another embodiment, the methods provide for ameliorating or reducing the symptoms of Guillain Barre Syndrome (GBS) by introducing a catheter apparatus through a spinal access site into a spinal CSF space of a patient; advancing the catheter apparatus through the spinal CSF space toward the brain so that a distal port and a proximal port on the catheter apparatus are disposed within the CSF space and spaced-apart by a preselected distance or adjusted to an appropriate distance; withdrawing CSF through one of said ports; removing at least one of cells and inflammatory mediators selected from the group consisting of C5a, TNF- α , IL-2, IL-6, interferon- γ , IgG, and endotoxins from the withdrawn CSF thereby conditioning the CSF; and returning the conditioned CSF through the other of said ports.

[0139] Further embodiments for treating Guillain Barre Syndrome are as discussed above and herein.

vii. Multiple Sclerosis (MS)

[0140] Multiple sclerosis (MS) is the most common demyelinating disease in humans and has an unknown etiology. However, it is widely accepted to be an autoimmune disease mediated by autoreactive T lymphocytes with specificity for myelin antigens. *See,*

5 Noseworthy, J. H. (1999). *Nature* 399(6738 Suppl): A40-7. The pathologic hallmark of the disease is the MS plaque, an area of white matter demyelination usually accompanied by inflammatory infiltrate composed of T lymphocytes, some B cells and plasma cells, activated macrophages or microglial cells. IgG and complement are localized primarily at the periphery of plaques. B lymphocyte clones accumulate in the CSF of MS patients and
10 patients with other neurological disorders. Anti- myelin-oligodendrocyte glycoprotein antibodies were detected in CSF from seven of the patients with MS, compared to two with other neurological diseases and one with tension headache. *See,* Hohlfeld, R. and H. Wekerle (2004). *Proc Natl Acad Sci U S A* 101 Suppl 2: 14599-606. Elevated numbers of CD4+ T helper cells can be found in the CSF during early exacerbations. Osteopontin is increased in
15 patients' plasma before and during relapses and was found to induce worsening autoimmune relapses and severe progression of myelinating diseases. *See,* Hohlfeld, R. and H. Wekerle (2004). *Proc Natl Acad Sci U S A* 101 Suppl 2: 14599-606. Current therapies are limited and often ineffective and include global immunosuppression mediated by steroids, interferon beta therapy, monoclonal antibody treatments and peptide fragments similar to myelin proteins.
20 CSF purification would have the advantage of depletion cell populations and alleviated the effects of MS exacerbations by: 1) removal of autoreactive CD4+ and CD8+ T cells, 2) reduction in the levels of pro-inflammatory cytokines and 3) reduction in the production of autoreactive antibodies by B cells. Depletion of these autoreactive cell populations also can reduce the recurrence of MS exacerbations, limit permanent damage caused by the
25 inflammation seen in an exacerbation, and prevent lesions that mark progression of the disease. By restricting this depletion to the CSF, the present systems and methods addresses these issues without many of the complications associated with steroid treatment or systemic immunosuppression.

[0141] Accordingly, the present methods provide for ameliorating or reducing the
30 symptoms of multiple sclerosis (MS) by reducing or eliminating the presence of one or more of T cells, B cells, anti-myelin antibodies and inflammatory mediators selected from the group consisting of TNF- α , IL-2, IL-6, interferon- γ in the CSF using the systems described herein. The methods comprise removing CSF from a patient, as described herein; removing

at least one of T cells, B cells, anti-myelin antibodies and inflammatory mediators selected from the group consisting of TNF- α , IL-2, IL-6, interferon- γ from the CSF, and returning the endogenous CSF to the patient, wherein the removing and returning steps are performed concurrently during at least a portion of the treatment. In some embodiments, the T cells,
 5 B cells, anti-myelin antibodies and inflammatory mediators selected from the group consisting of TNF- α , IL-2, IL-6, interferon- γ are removed from the CSF using one or more of an immunoaffinity column, a size exclusion column, an anionic exchange column, a cationic exchange column and a Protein A or Protein G column.

[0142] In another embodiment, the methods provide for ameliorating or reducing the
 10 symptoms of multiple sclerosis (MS) by introducing a catheter apparatus through a spinal access site into a spinal CSF space of a patient; advancing the catheter apparatus through the spinal CSF space toward the brain so that a distal port and a proximal port on the catheter apparatus are disposed within the CSF space and spaced-apart by a preselected distance or adjusted to an appropriate distance; withdrawing CSF through one of said ports; removing at
 15 least one of T cells, B cells, anti-myelin antibodies and inflammatory mediators selected from the group consisting of TNF- α , IL-2, IL-6, interferon- γ from the withdrawn CSF thereby conditioning the CSF; and returning the conditioned CSF through the other of said ports.

[0143] Further embodiments for treating multiple sclerosis (MS) are as discussed above and herein.

20 viii. Stroke

[0144] Stroke occurs when a blood clot blocks an artery or a blood vessel breaks, interrupting blood flow to an area of the brain; brain cells then begin to die and brain damage occurs. Free radical injury is implicated in pathogenesis of stroke. CSF enolase was raised in patients with transient ischemic attacks and patients with complete strokes. *See*, McCulloch,
 25 J. and D. Dewar (2001). *Proc Natl Acad Sci U S A* 98(20): 10989-91. A high cerebrospinal fluid enolase was always associated with a poor prognosis. Endothelin 1 (ET-1), a highly potent endogenous vasoactive peptide, exerts a sustained vasoconstrictive effect on cerebral vessels. *See*, Mascia, L., L. Fedorko, et al. (2001). *Stroke* 32(5): 1185-90; and Kessler, I. M., Y. G. Pacheco, et al. (2005). *Surg Neurol* 64 Suppl 1: S1:2-5; discussion S1:5. Elevation of
 30 ET-1 in plasma has been reported 1 to 3 days after ischemic stroke. Mean CSF concentration of ET-1 in the CSF of stroke patients was 16.06 ± 4.9 pg/mL, compared with 5.51 ± 1.47 pg/mL in the control group ($P < .001$). *See*, Mascia, L., L. Fedorko, et al. (2001). *Stroke* 32(5): 1185-

90; and Kessler, I. M., Y. G. Pacheco, et al. (2005). *Surg Neurol* 64 Suppl 1: S1:2-5; discussion S1:5. Current stroke management is ineffective and includes symptomatic treatment (surgery, hospital care, and rehabilitation) or carries a risk of brain hemorrhage (cerebral angioplasty and use of tissue plasminogen activator (tPA) to dissolve acute clot in

5 vessel). Similarly, traumatic brain injury (TBI) or spinal cord injury (SCI) occurs when sudden trauma affects the brain or spinal cord following falls, motor vehicle accidents, assaults etc. Current treatment of TBI and SCI focuses on increasing independence in everyday life and rehabilitation (i.e. individual therapy). Moderate hypothermia is thought to limit deleterious metabolic processes that can exacerbate injury. CSF processing would
10 allow for not only the removal of neuroinflammatory components such as enolase, ET-1 and free radicals but provide selective cooling to the CNS which is expected to be faster and more effective than systemic cooling, which is limited by shivering and the danger of severe cardiac arrhythmias.

[0145] Accordingly, the present methods provide for ameliorating or reducing the
15 symptoms of stroke, traumatic brain injury (TBI), spinal cord injury (SCI) by reducing or eliminating the presence of one or more of endothelin and enolase or other inflammatory mediators in the CSF using the systems described herein. The methods comprise removing CSF from a patient, as described herein; removing at least one of endothelin and enolase from the CSF, and returning the endogenous CSF to the patient, wherein the removing and
20 returning steps are performed concurrently during at least a portion of the treatment. In some embodiments, the endothelin and enolase or other inflammatory mediators are removed from the CSF using one or more of an immunoaffinity column, a size exclusion column, an anionic exchange column, a cationic exchange column and a Protein A or Protein G column. In some embodiments, the removed CSF is cooled to below physiological temperatures.

25 [0146] In another embodiment, the methods provide for ameliorating or reducing the symptoms of stroke, TBI, SCI by introducing a catheter apparatus through a spinal access site into a spinal CSF space of a patient; advancing the catheter apparatus through the spinal CSF space cranially toward the brain so that a distal port and a proximal port on the catheter apparatus are disposed within the CSF space and spaced-apart by a preselected distance or
30 adjusted to an appropriate distance; withdrawing CSF through one of said ports; removing at least one of endothelin and enolase or other inflammatory mediators from the withdrawn CSF and/or cooling the CSF to varying degrees thereby conditioning the CSF; and returning the conditioned CSF through the other of said ports.

[0147] Further embodiments for treating stroke are as discussed above and herein.

[0148] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

- 1 1. A method for conditioning cerebrospinal fluid (CSF) in a patient, said
2 method comprising:
3 removing CSF from a first location in a CSF space of the patient;
4 conditioning the removed CSF; and
5 returning the conditioned CSF to the patient at a second location in the CSF
6 space;
7 wherein the removing and returning steps are performed concurrently during
8 at least a portion of a conditioning treatment.
- 1 2. A method as in claim 1, wherein the CSF is removed and returned at
2 substantially the same flow rate.
- 1 3. A method as in claim 2, wherein the flow rate is in the range from
2 0.04 ml/min to 30 ml/min.
- 1 4. A method as in claim 3, wherein the volume of CSF removed from the
2 patient never exceeds 40 ml.
- 1 5. A method as in claim 1, wherein the distance between the first location
2 and the second location is at least 4 cm.
- 1 6. A method as in claim 5, wherein the first location is at S1 or above and
2 the second location is at L3 or above.
- 1 7. A method as in claim 6, wherein the second location is in the cervical
2 CSF space.
- 1 8. A method as in claim 6, wherein the second location is in a ventricle.
- 1 9. A method as in claim 1, wherein the flow directions of removing and
2 returning CSF are periodically reversed so that CSF is returned to the first location and
3 removed from a second location during a portion of the treatment.
- 1 10. A method as in claim 9, wherein the flow reversal is a pulse to
2 dislodge debris from removal or return ports.

1 11. A method as in claim 1, further comprising mixing the conditioned
2 CSF with endogenous CSF as the conditioned CSF is returned to the CSF space.

1 12. A method as in claim 11, wherein mixing comprises inducing a
2 turbulent flow as the conditioned CSF is returned.

1 13. A method as in claim 1, wherein conditioning comprises removing a
2 targeted molecule.

1 14. A method as in claim 13, further comprising the step of isolating the
2 targeted molecule.

1 15. A method as in claim 1, wherein conditioning comprises one or more
2 separation processes selected from the group consisting of biospecific affinity,
3 immunoaffinity, cationic exchange, anionic exchange, hydrophobicity and size exclusion.

1 16. A method as in claim 1, wherein the conditioning step is performed
2 externally to the patient's body.

1 17. A method as in claim 1, wherein the conditioning step is performed
2 using a conditioning unit implanted in the patient's body.

1 18. A method for conditioning cerebrospinal fluid (CSF) in a patient, said
2 method comprising:
3 introducing a catheter apparatus through a lumbar access site into a spinal CSF
4 space of the patient;
5 advancing the catheter apparatus through the spinal CSF space toward the
6 brain so that a distal port and a proximal port on the catheter apparatus are disposed within
7 the CSF space and spaced-apart by a preselected distance;
8 withdrawing CSF through one of said ports;
9 conditioning the withdrawn CSF; and
10 returning the conditioned CSF through the other of said ports.

1 19. A method as in claim 18, wherein the distal port on the catheter is
2 advanced to a location in the cervical CSF space.

1 20. A method as in claim 18, wherein the distal port on the catheter is
2 advanced to a location in the cranial subarachnoid space.

1 21. A method as in claim 18, wherein the distal port and proximal port are
2 spaced-apart by a distance of at least 4 cm.

1 22. A method as in claim 18, wherein the catheter apparatus consists
2 essentially of a single catheter body having a lumen connected to the distal port and a
3 separate lumen connected to the proximal port.

1 23. A method as in claim 18, wherein the CSF is returned under conditions
2 which enhance mixing of the returned CSF with the unconditioned CSF.

1 24. A method as in claim 23, wherein the conditions that enhance mixing
2 or the returned CSF include one or more selected from the group consisting of directed
3 outflow, high pressure injection, injection through multiple ports, a helical catheter, a
4 T-catheter, bellows, ribbed catheter, fins and balloons.

1 25. A method for conditioning cerebrospinal fluid in a patient, said method
2 comprising:

3 introducing a catheter apparatus into a brain ventricle;
4 adjusting spacing between a pair of ports on the catheter apparatus so one port
5 lies on one side of the ventricle and the other port lies on another side of the ventricle;
6 withdrawing CSF through one of said ports;
7 conditioning the withdrawn CSF; and
8 returning the conditioned CSF to the ventricle through the other of said ports.

1 26. A method as in claim 25, wherein the spacing between the pair of ports
2 is at least 4 cm.

1 27. A method as in claim 25, wherein each port is in a different ventricle.

1 28. A method as in claim 25, wherein both ports are in the same ventricle.

1 29. A method as in claim 25, wherein adjusting the spacing between the
2 pair of ports comprises axially translating a pair of tubular members relative to each other.

1 30. A system for conditioning cerebrospinal fluid (CSF) in a patient, said
2 system comprising:
3 a catheter assembly having a first lumen with a distal port and a second lumen
4 with a proximal port, said catheter being adapted to be introduced in a CSF space and said
5 ports being spaced axially apart;
6 a pump connectable between the first and second lumens to induce a flow of
7 CSF therebetween; and
8 a conditioning component connectable between the first and second lumens to
9 condition the CSF flowing therebetween.

1 31. A system as in claim 30, wherein said catheter assembly consists
2 essentially of a single tubular member having the first lumen and distal port and the second
3 lumen and proximal port fixedly disposed therein.

1 32. A system as in claim 30, wherein said catheter comprises a first tubular
2 member having the first lumen and the distal port therein and a second tubular member
3 having the second lumen and proximal port therein.

1 33. A system as in claim 32, wherein the first and second tubes may be
2 axially translated relative to each other to adjust the distance therebetween.

1 34. A system as in claim 30, wherein the pump has a flow rate adjustable
2 between 0.04 ml/min to 30 ml/min.

1 35. A system as in claim 34, wherein the pump comprises a peristaltic
2 pump which is isolated from the CSF flow.

1 36. A system as in claim 30, wherein the condition component is selected
2 from the group consisting of biospecific affinity, immunoaffinity, cationic exchange, anionic
3 exchange, hydrophobicity and size exclusion.

1 37. A system as in claim 30, wherein the system has a CSF retention
2 volume below 40 ml.

1 38. A system as in claim 30, wherein the system is implantable.

1 39. A method for ameliorating the symptoms of Alzheimer's Disease in a
2 patient, said method comprising:

3 removing CSF from a first location in a CSF space of the patient;
4 removing at least one of beta-amyloid or tau proteins from the removed CSF,
5 thereby conditioning the CSF; and
6 returning the conditioned CSF to the patient at a second location in the CSF
7 space;

8 wherein the removing and returning steps are performed concurrently during
9 at least a portion of a conditioning treatment.

1 40. A method for ameliorating the symptoms of Parkinson's Disease in a
2 patient, said method comprising:

3 removing CSF from a first location in a CSF space of the patient;
4 removing at least one of alpha-synuclein fibrils and oligomers from the
5 removed CSF, thereby conditioning the CSF; and
6 returning the conditioned CSF to the patient at a second location in the CSF
7 space;

8 wherein the removing and returning steps are performed concurrently during
9 at least a portion of a conditioning treatment.

1 41. A method for ameliorating the symptoms of Amyotrophic lateral
2 sclerosis (ALS) in a patient, said method comprising:

3 removing CSF from a first location in a CSF space of the patient;
4 removing at least one of insoluble superoxide dismutase-1 (SOD1), glutamate,
5 neurofilament protein, and anti-GM1 ganglioside antibodies from the removed CSF, thereby
6 conditioning the CSF; and

7 returning the conditioned CSF to the patient at a second location in the CSF
8 space;

9 wherein the removing and returning steps are performed concurrently during
10 at least a portion of a conditioning treatment.

1 42. A method for ameliorating the symptoms of cerebral vasospasm in a
2 patient, said method comprising:

3 removing CSF from a first location in a CSF space of the patient;

removing at least one of erythrocytes, hemoglobin, oxyhemoglobin and endothelin from the removed CSF, thereby conditioning the CSF; and
returning the conditioned CSF to the patient at a second location in the CSF space;
wherein the removing and returning steps are performed concurrently during at least a portion of a conditioning treatment.

43. A method for ameliorating the symptoms of encephalitis in a patient, said method comprising:
removing CSF from a first location in a CSF space of the patient;
removing at least one of tumor necrosis factor-alpha (TNF α) and IgG from the removed CSF, thereby conditioning the CSF; and
returning the conditioned CSF to the patient at a second location in the CSF space;
wherein the removing and returning steps are performed concurrently during at least a portion of a conditioning treatment.

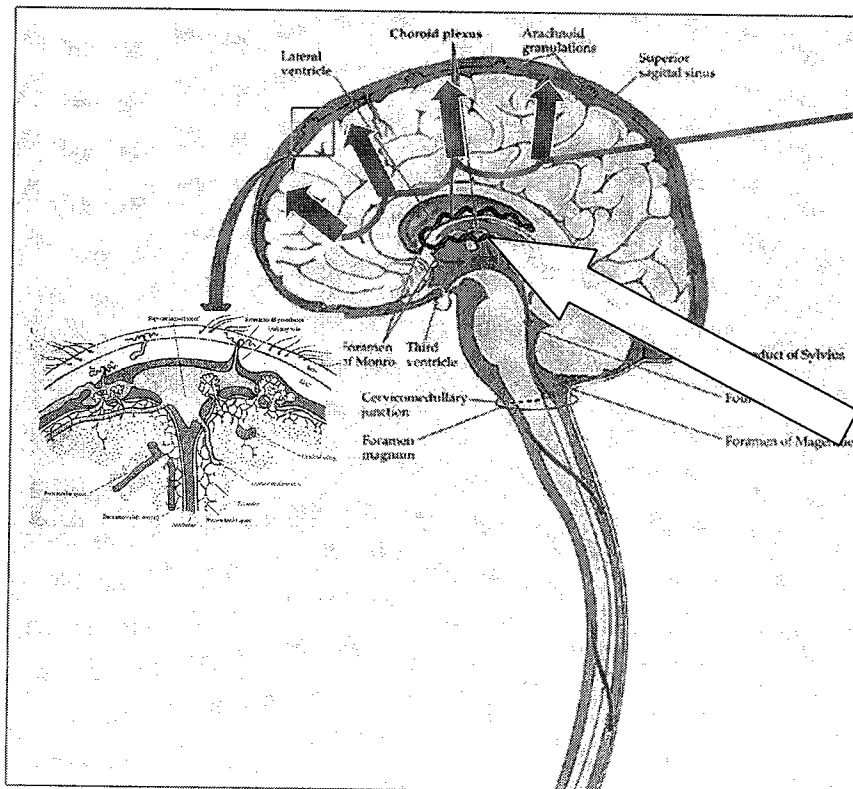
44. A method for ameliorating the symptoms of Guillain Barre Syndrome (GBS) in a patient, said method comprising:
removing CSF from a first location in a CSF space of the patient;
removing at least one of cells and inflammatory mediators selected from the group consisting of C5a, TNF α , IL-2, IL-6, interferon- γ , IgG, and endotoxins from the removed CSF, thereby conditioning the CSF; and
returning the conditioned CSF to the patient at a second location in the CSF space;
wherein the removing and returning steps are performed concurrently during at least a portion of a conditioning treatment.

45. A method for ameliorating the symptoms of Multiple Sclerosis (MS) in a patient, said method comprising:
removing CSF from a first location in a CSF space of the patient;
removing at least one of T cells, B cells, anti-myelin antibodies and inflammatory mediators selected from the group consisting of TNF- α , IL-2, IL-6, interferon- γ from the removed CSF, thereby conditioning the CSF; and

7 returning the conditioned CSF to the patient at a second location in the CSF
8 space;
9 wherein the removing and returning steps are performed concurrently during
10 at least a portion of a conditioning treatment.

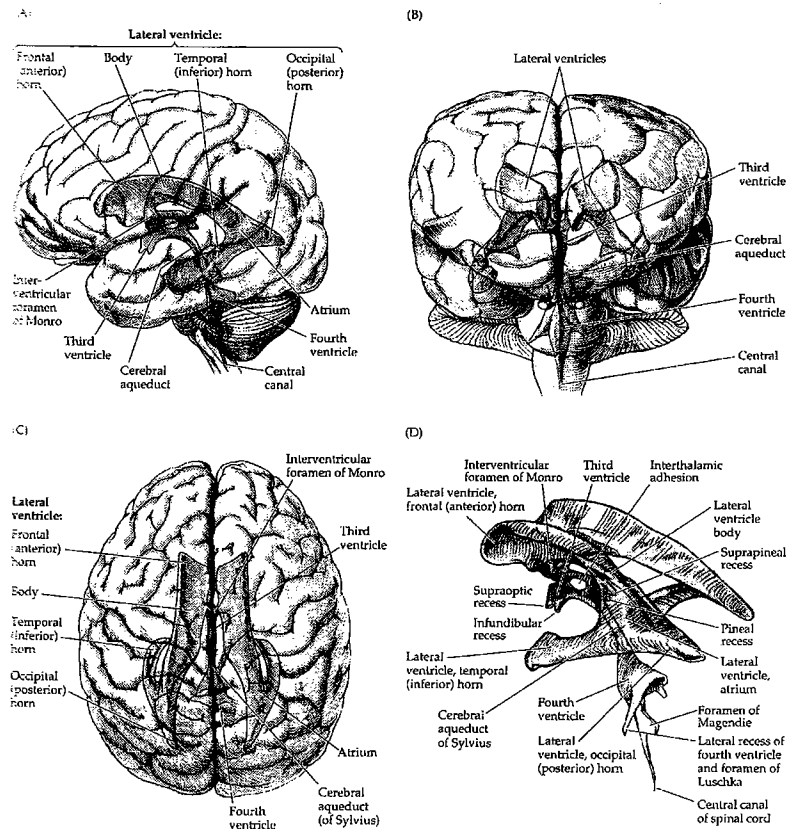
1 46. A method for ameliorating the symptoms of stroke in a patient, said
2 method comprising:
3 removing CSF from a first location in a CSF space of the patient;
4 removing at least one of endothelin and enolase from the removed CSF,
5 thereby conditioning the CSF; and
6 returning the conditioned CSF to the patient at a second location in the CSF
7 space;
8 wherein the removing and returning steps are performed concurrently during
9 at least a portion of a conditioning treatment.

1 47. The method of claim 46, further comprising the step of cooling the
2 CSF.

Figure 1

“Endogenous pathogens” :
neurotoxic molecules
released from brain
tissue into CSF

“Exogenous pathogens” :
cells [and neurotoxic
molecules] from the
peripheral circulation
into CSF

Figure 2**Figure 5.11 Brain Ventricles**

(A) Ventricles viewed from lateral surface of brain. (B) Ventricles viewed from anterior surface of brain. (C) Ventricles viewed from superior surface of brain. (D) Details of ventricular structure.

Figure 3

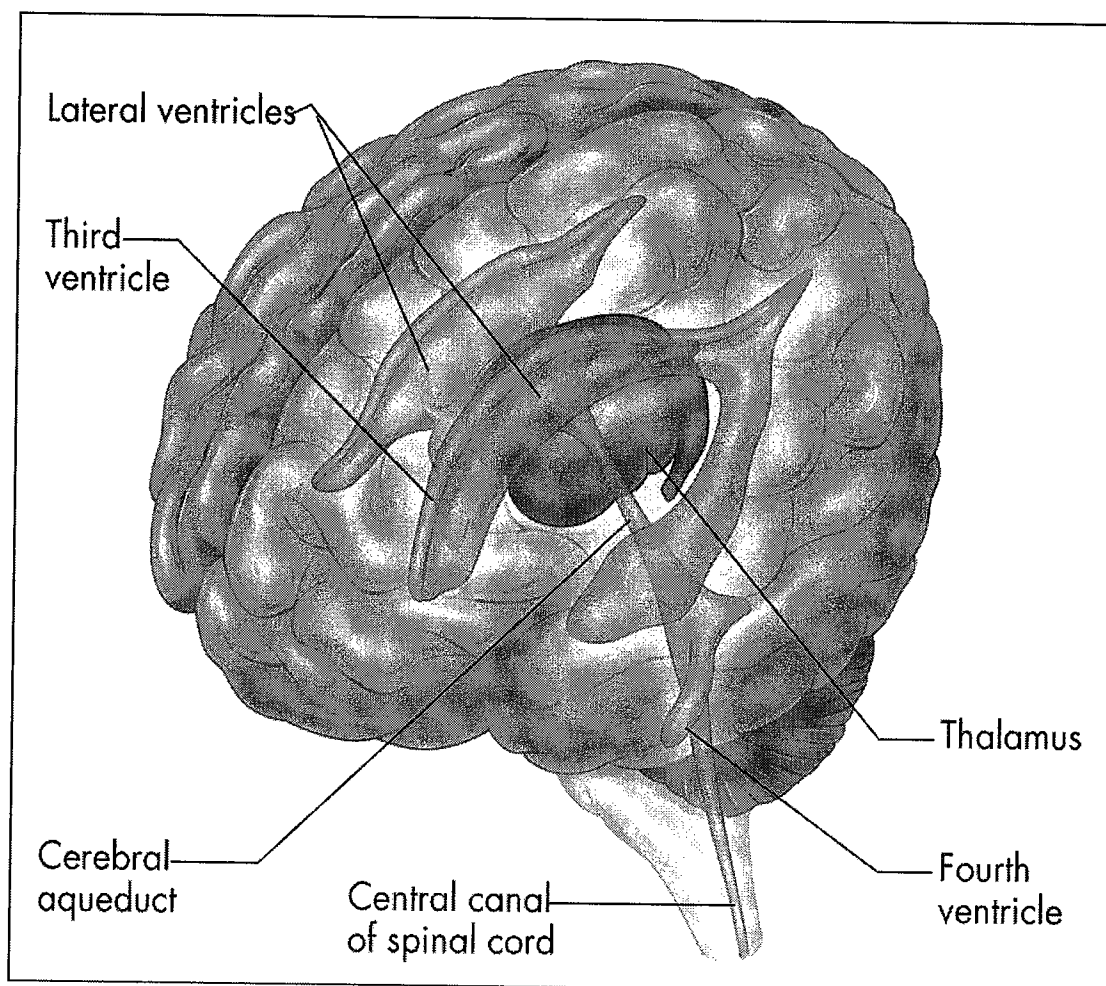


Figure 4

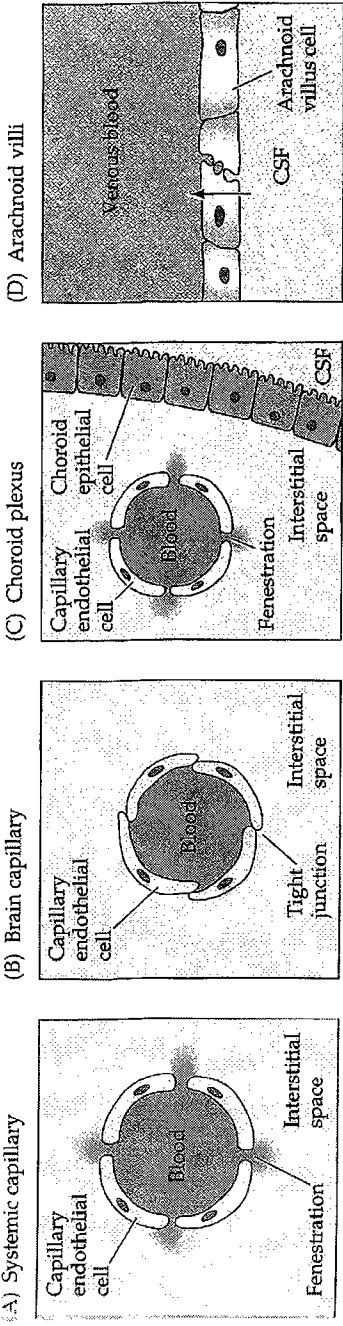


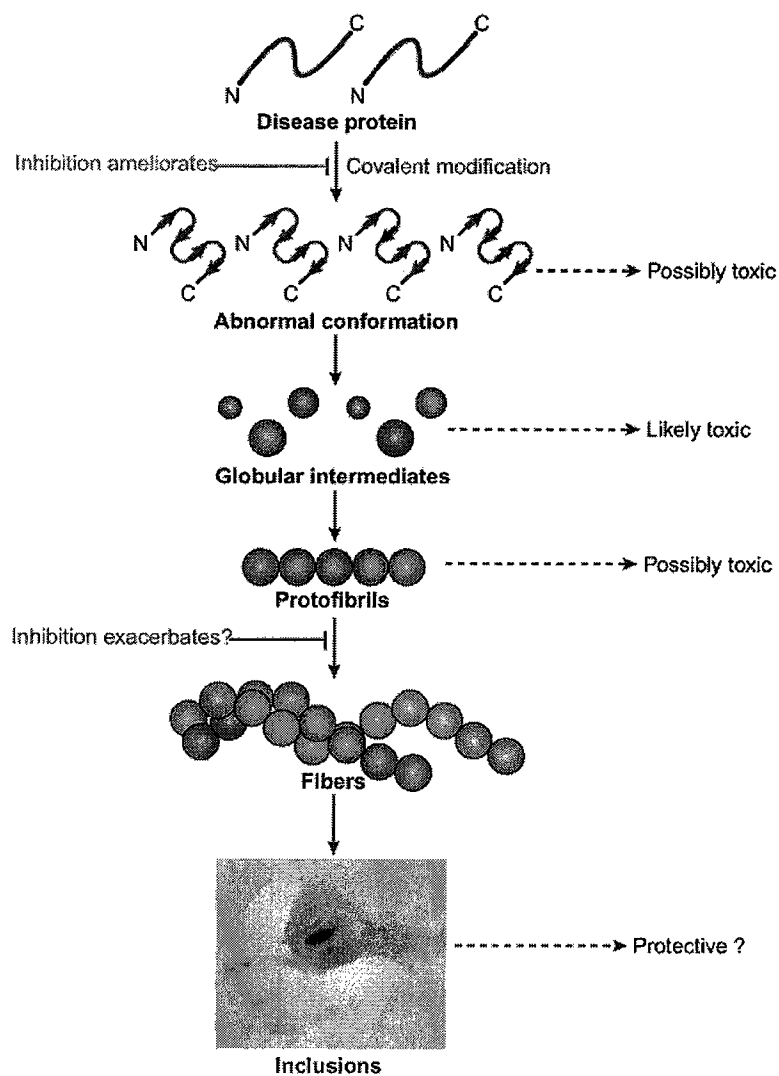
Figure 5

Figure 6A

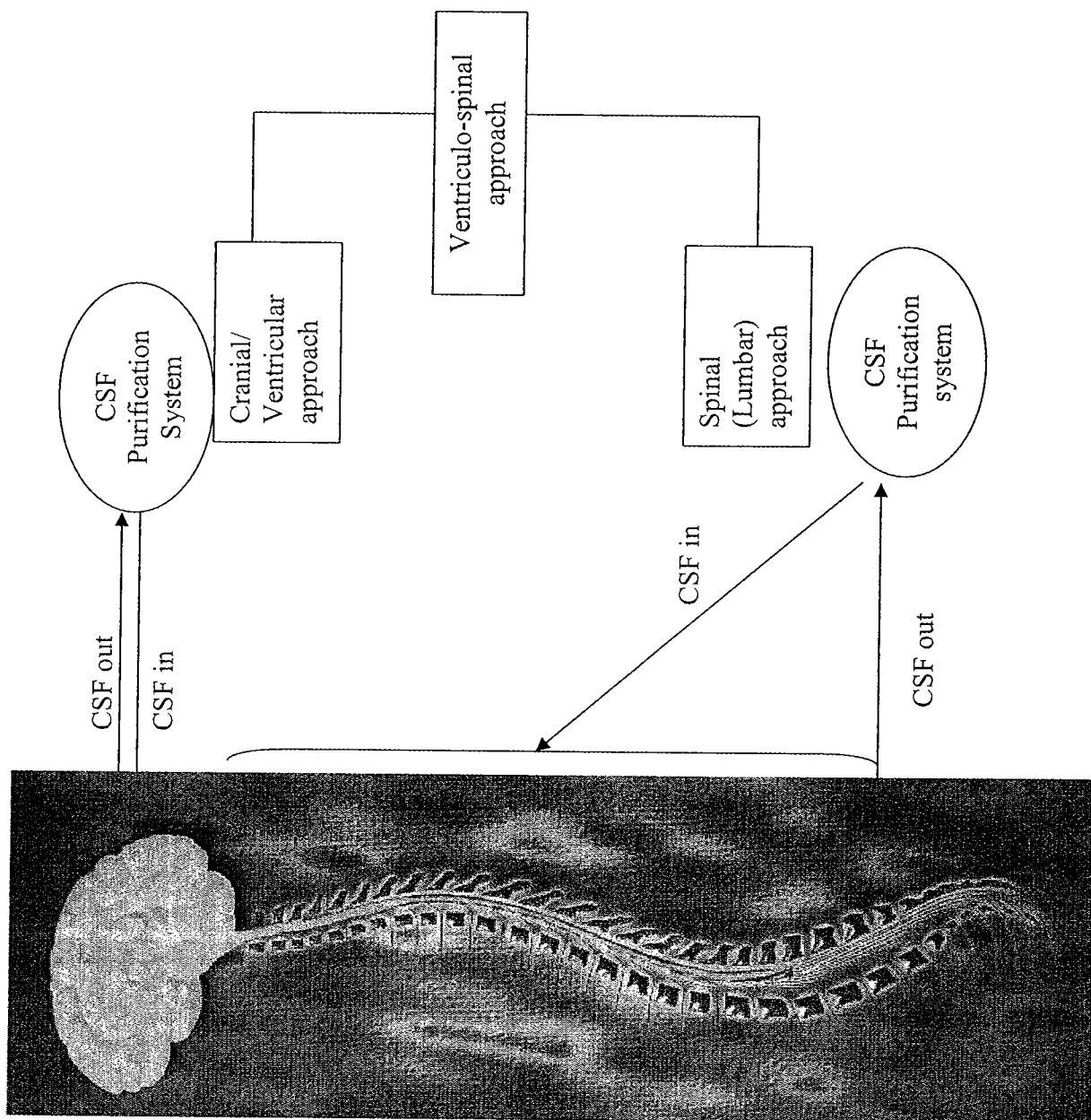


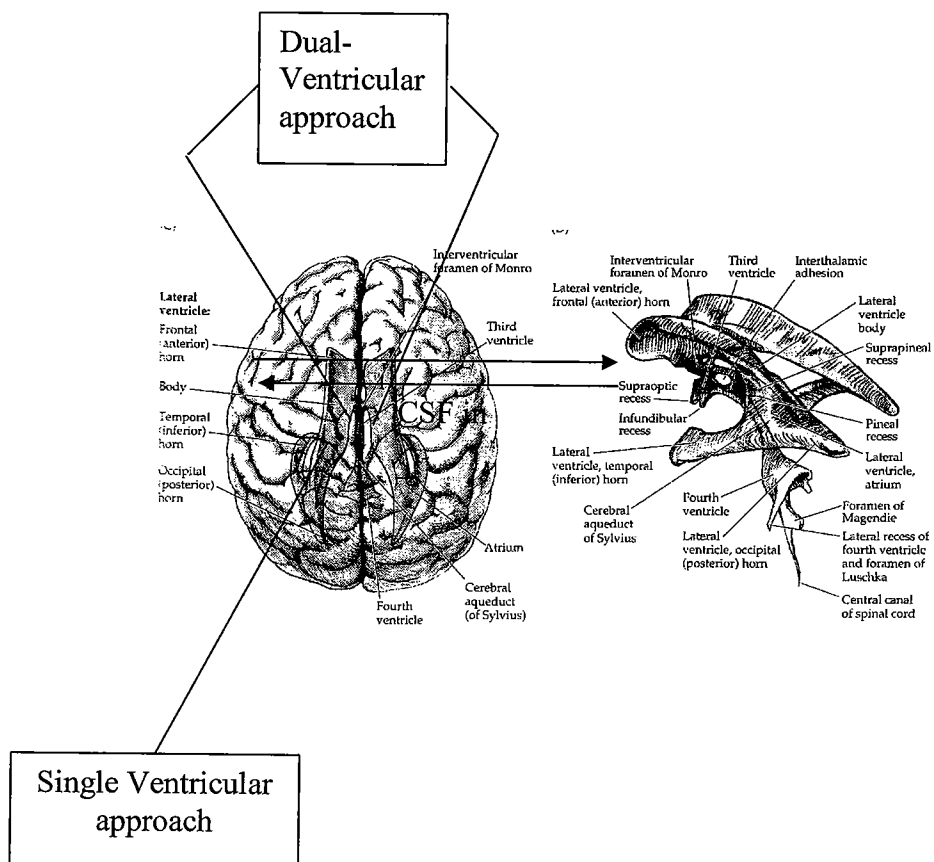
Figure 6B

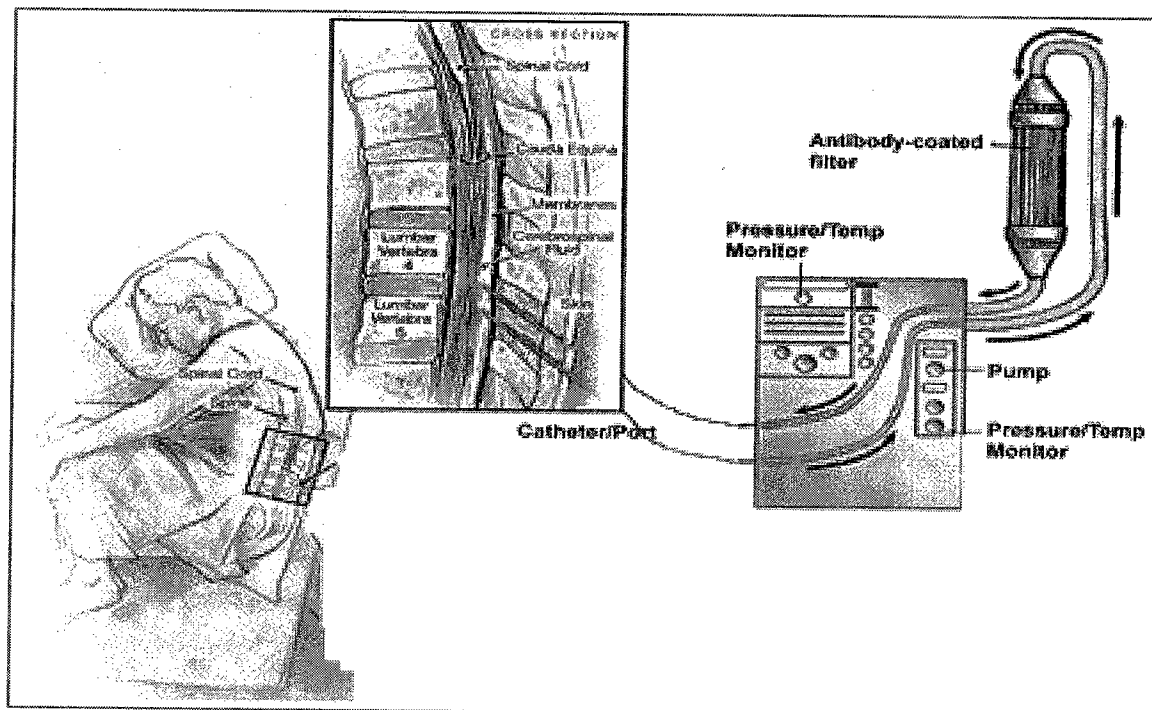
Figure 6C

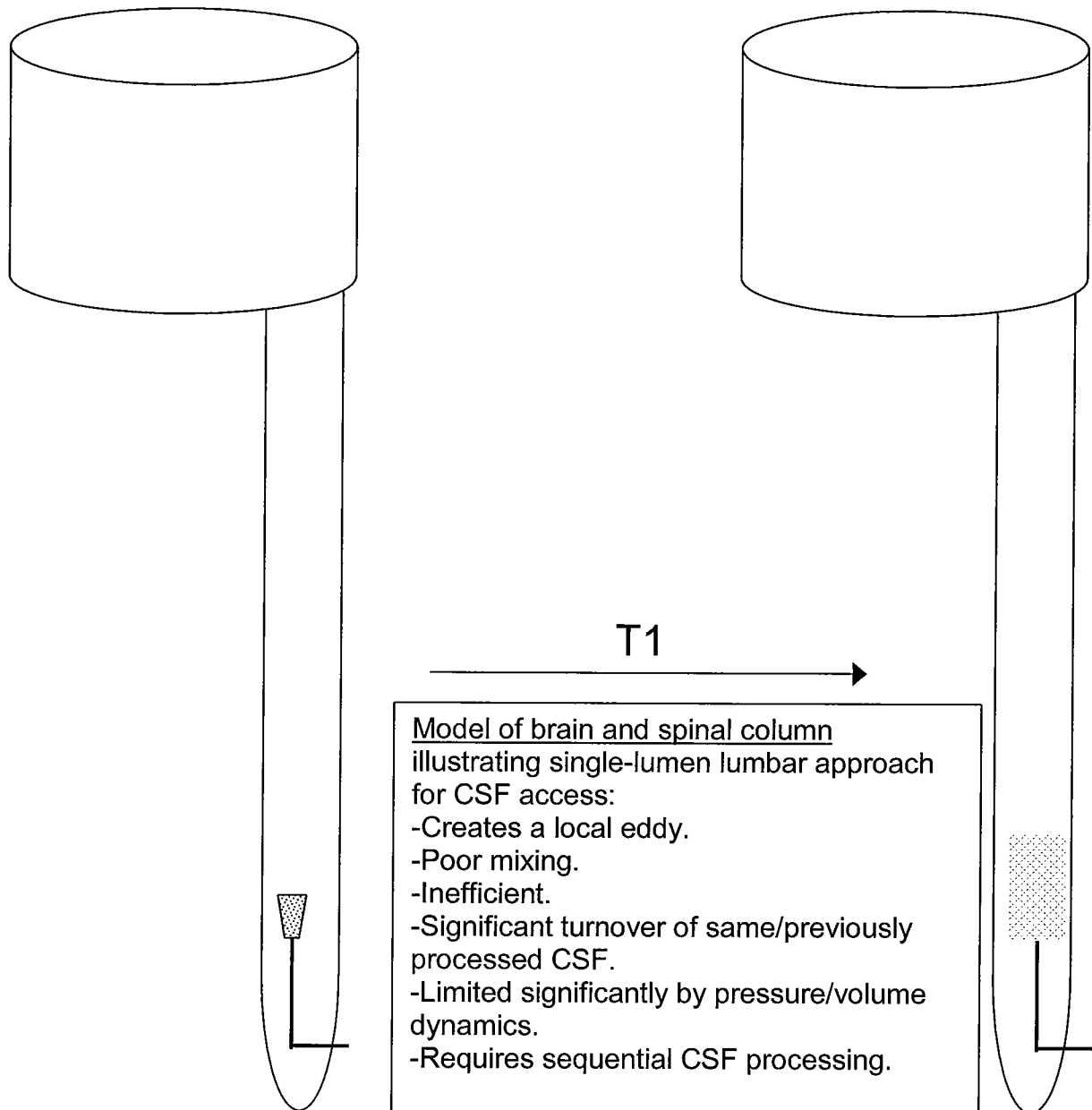
Figure 7

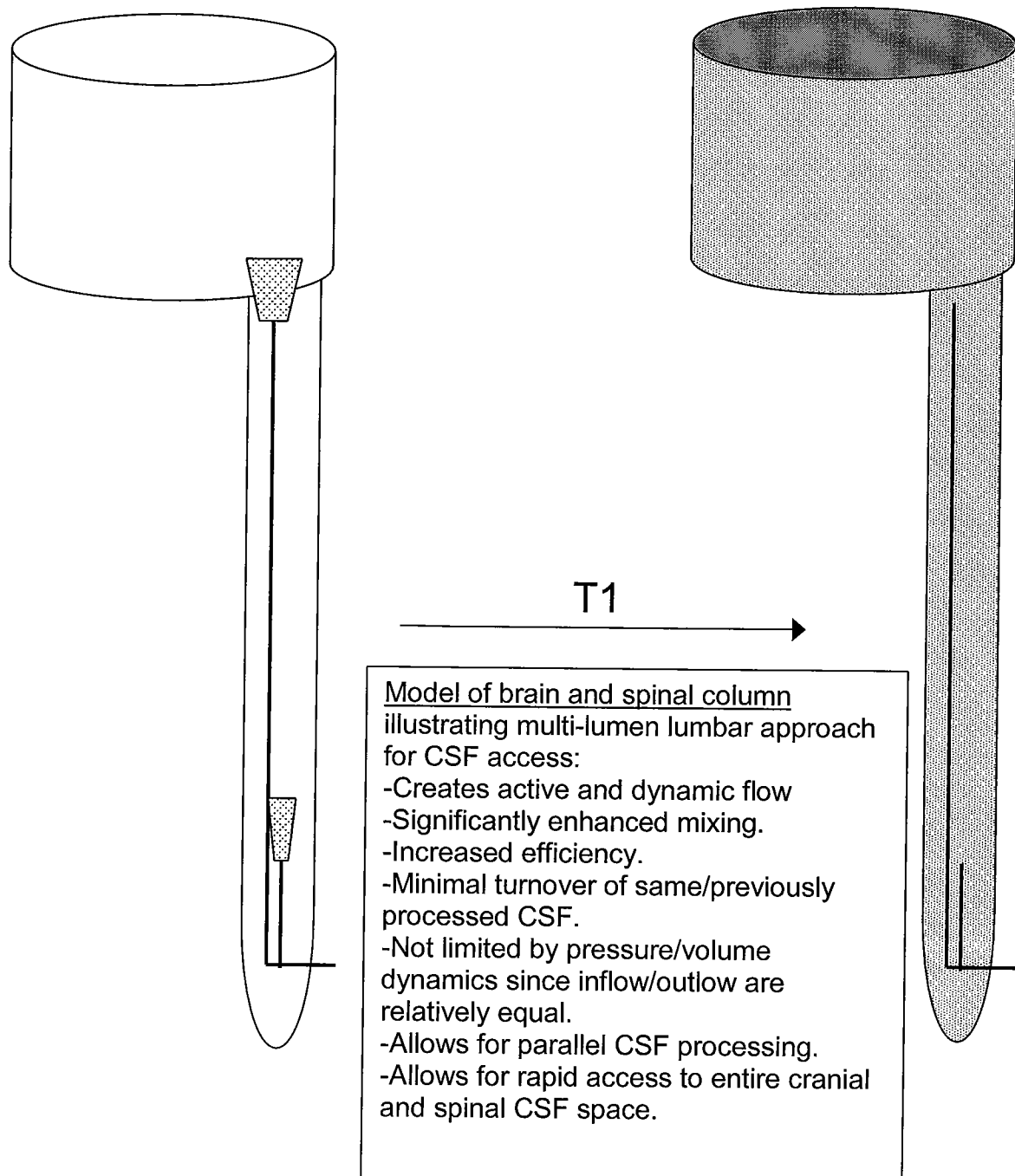
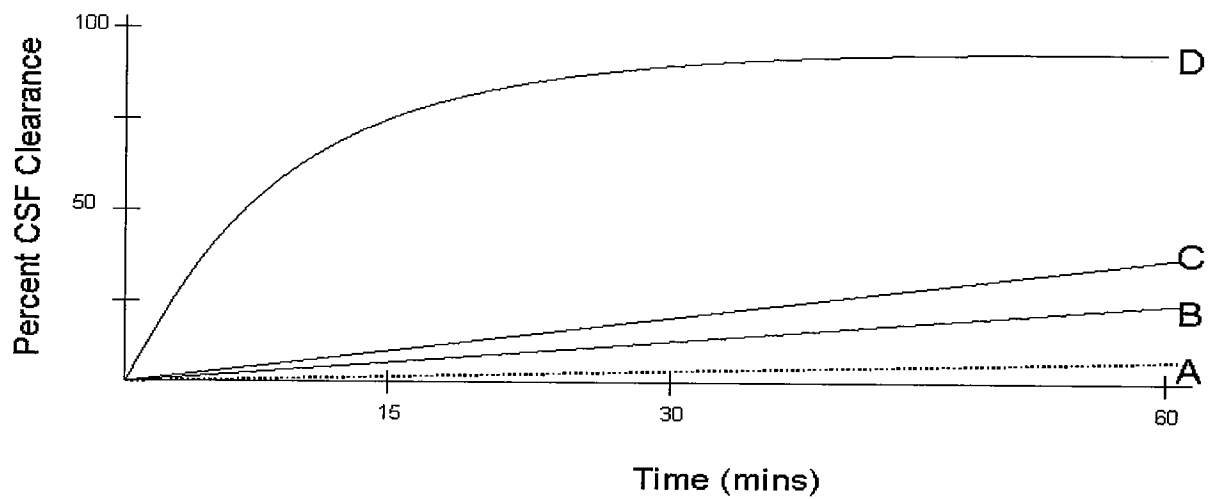
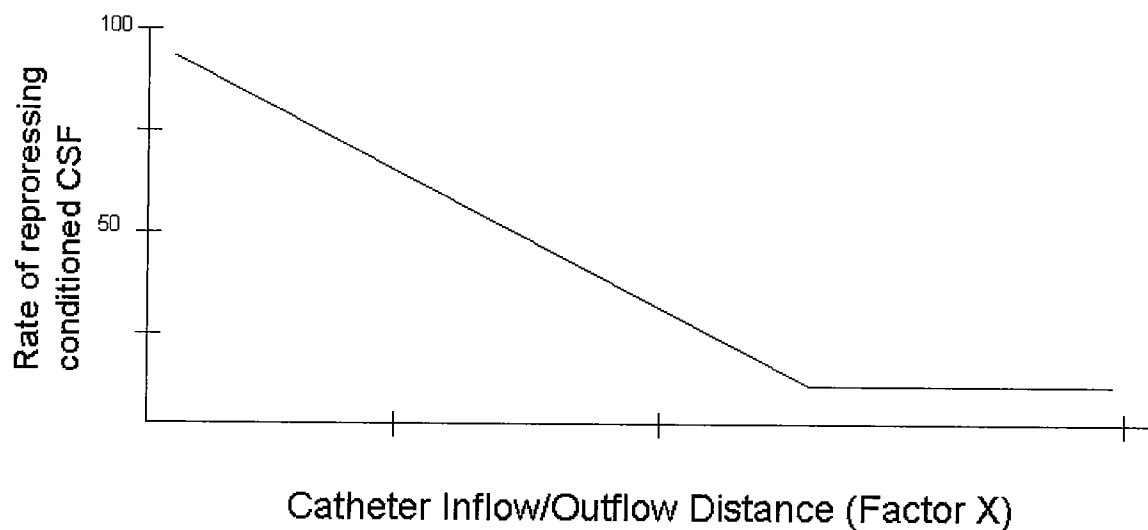
Figure 8A

Figure 8**B**

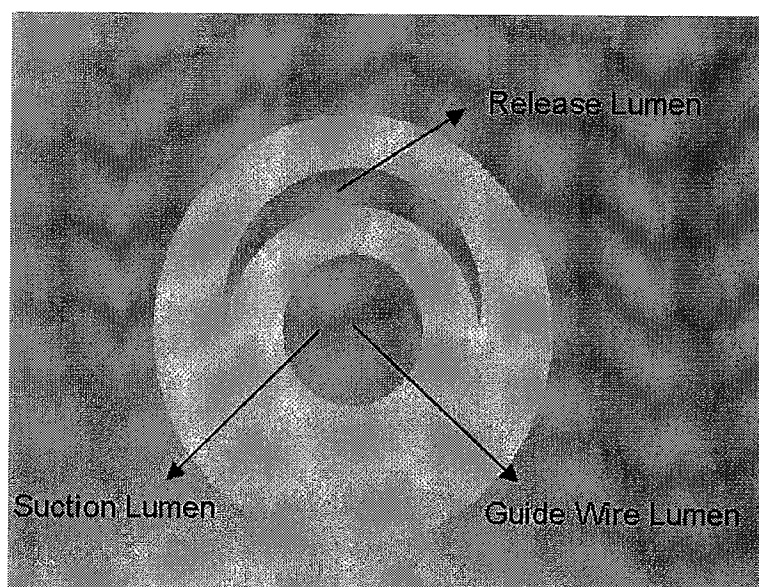
A= Diffusion
B= Single lumen catheter
C= Multilumen catheter with inflow/outflow directly adjacent
D= Multilumen catheter with inflow/out sufficient to create efficient CSF mixing

C

Factor X is based on a number factors and is largely related to size of separation based on distance between inflow and outflow, however can also be affected by a number of other factors including size, direction, flow rate, temperature, patient angle, gravity, number of lumens.

Figure 9

A



B

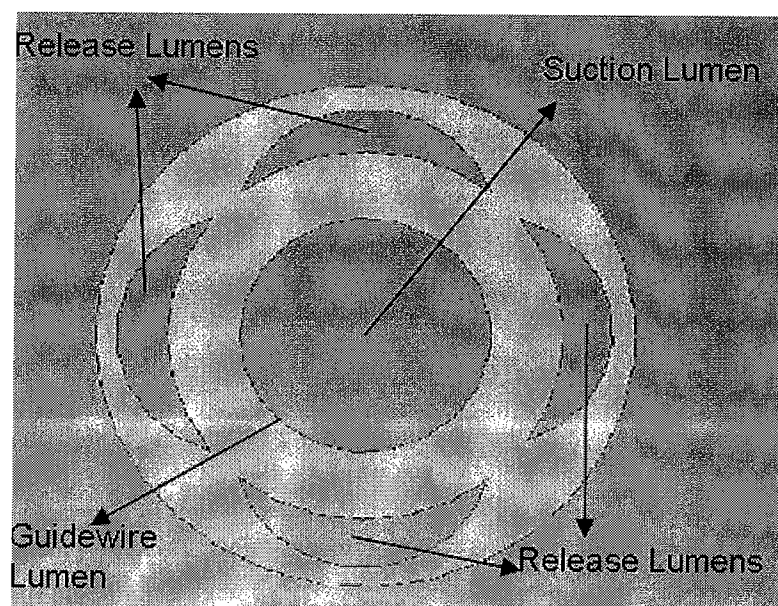
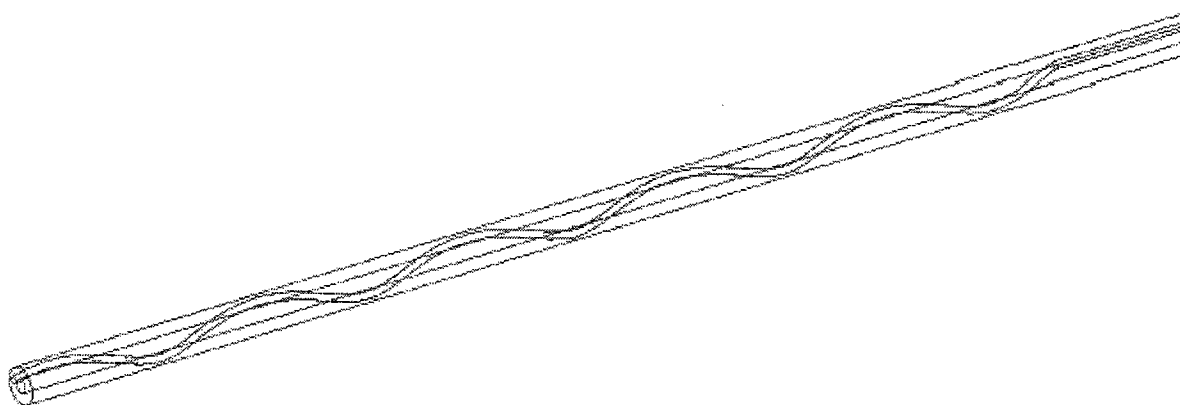


Figure 10

A



B

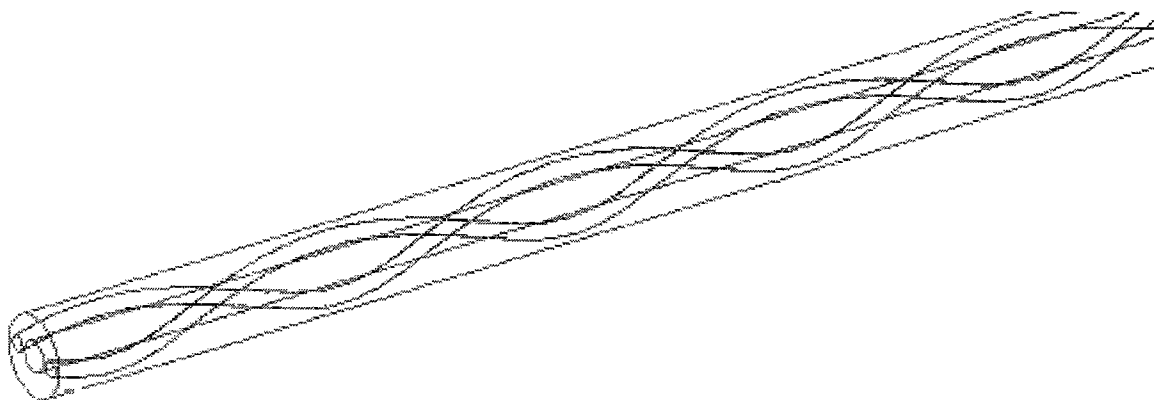
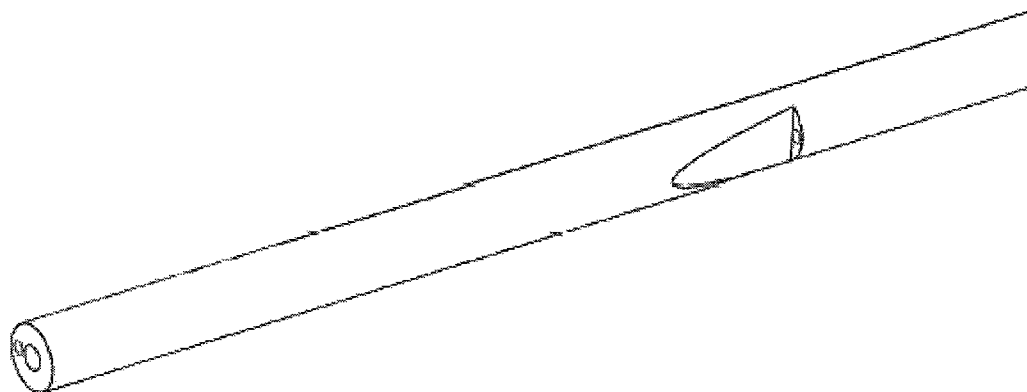


Figure 11

A



B

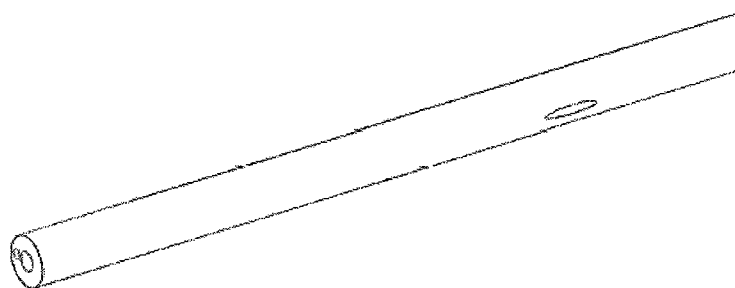
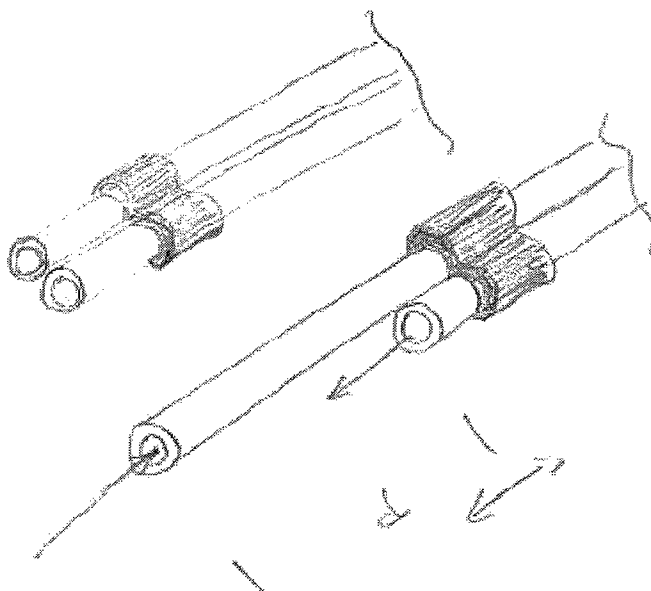


Figure 12

A



B



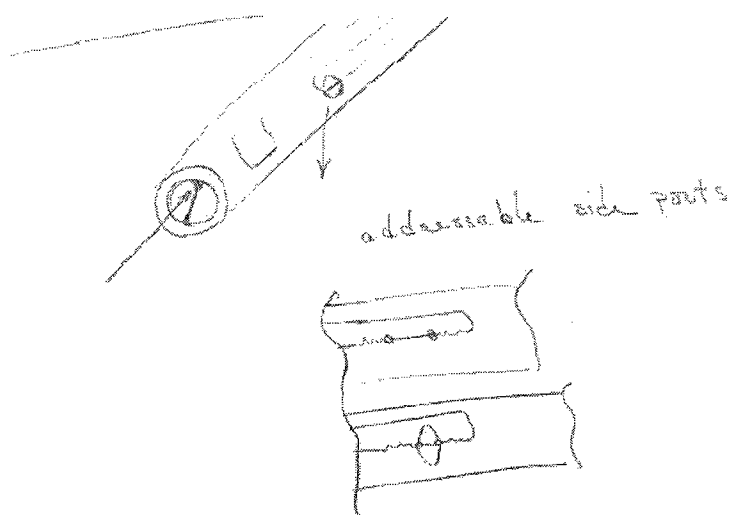
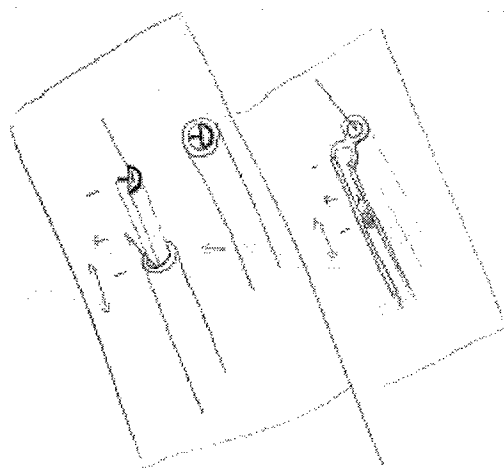
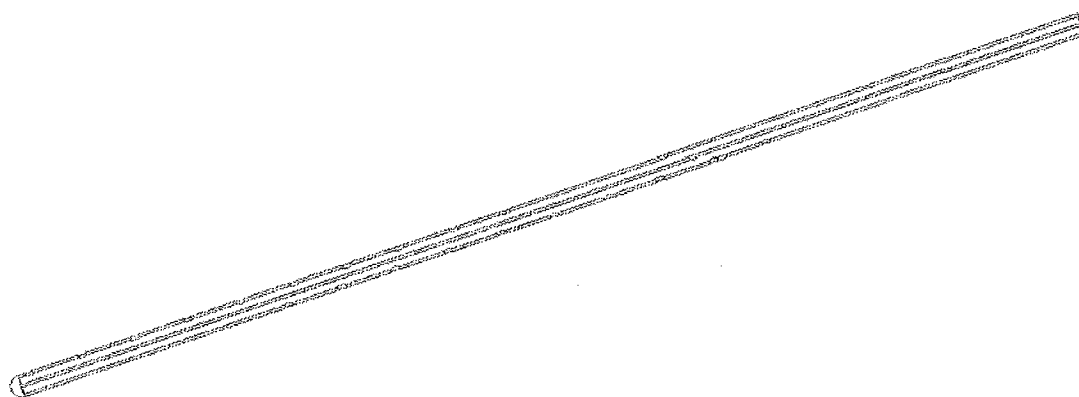
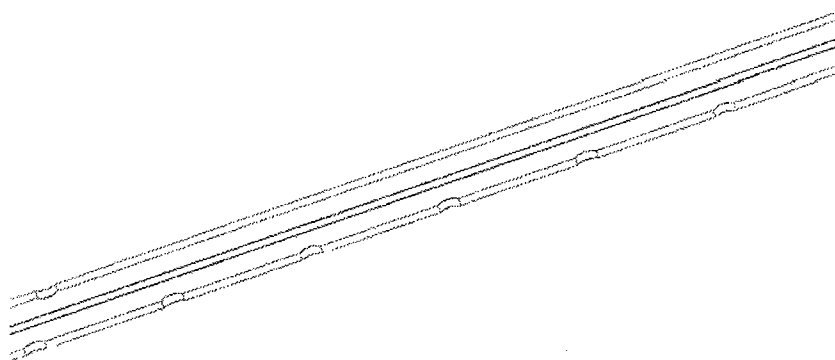
Figure 13**A****B**

Figure 14

A



B



C

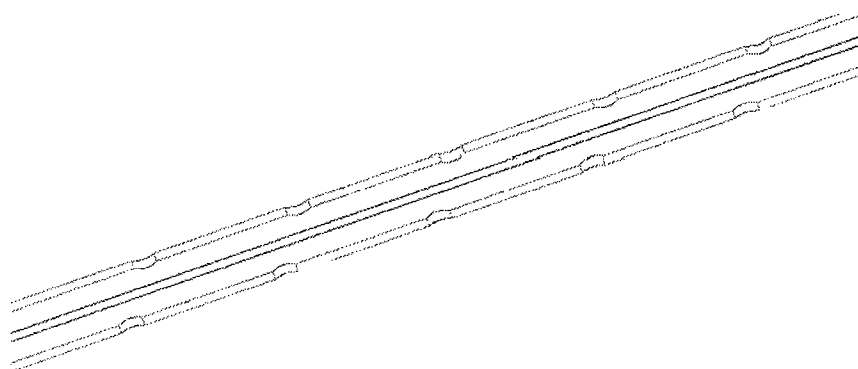
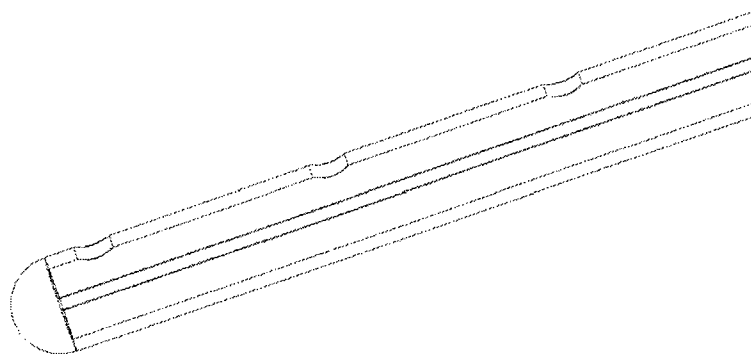
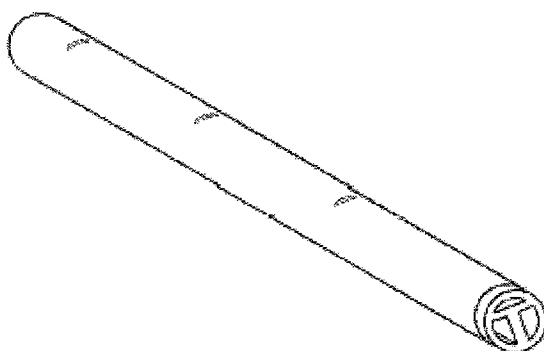


Figure 15

A



B



C

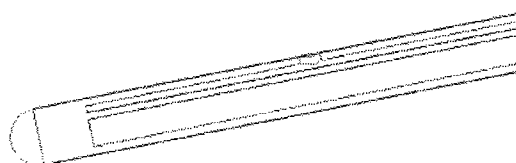
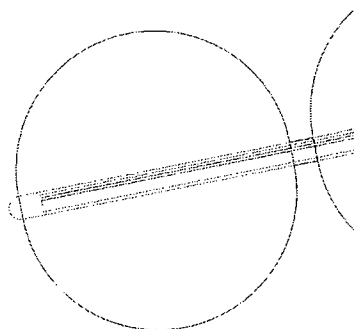
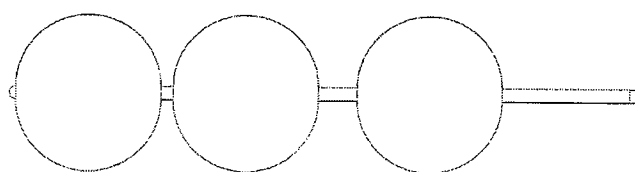


Figure 16

A



B



C

