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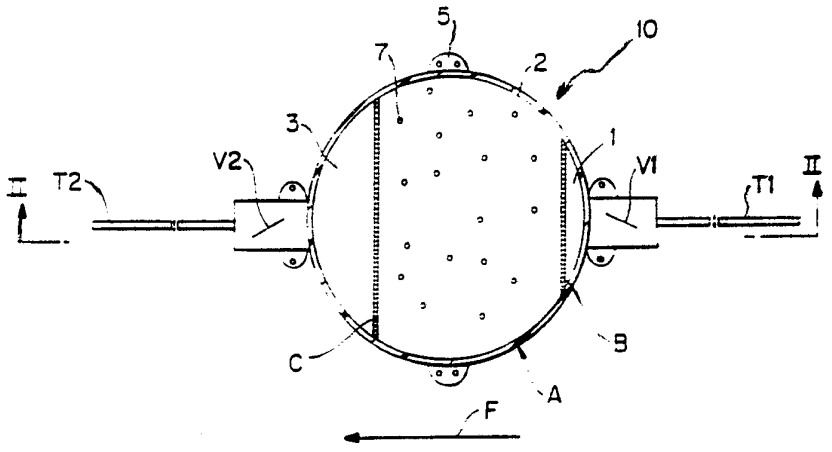
(54) Title: SPINAL FLUID DRIVEN ARTIFICIAL ORGAN



(57) Abstract

The present invention concerns a spinal fluid driven artificial organ device and methods for its use. The device (10) has a tripartite chamber with three sections. A micropore filter (B) separates chamber section (1) from chamber section (2) and a micropore filter (c) separates chamber section (2) from chamber section (3). CSF enters chamber section (1) via an inlet tube (T1) and an one way valve (V1). Micropore filter (B) allows entry of CSF into chamber section (2) but does not allow exit of any cells from chamber section (2) into chamber section (1). Micropore filter (c) allows free passage of CSF from chamber section (2) into chamber section (3) and prevents any cells in chamber section (2) from entering chamber section (3). The CSF flow exits chamber section (3) via an one way valve (V2) an an outlet tube (T2). The outlet tube (T2) delivers the CSF to the desired location.

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SPINAL FLUID DRIVEN ARTIFICIAL ORGAN

Background of the Invention

The present invention concerns a spinal fluid driven artificial organ device and a method for its use. In particular, this artificial organ, when it contains pancreatic islet cells, can be utilized to treat Type I diabetes mellitus. In addition, the artificial organ can be utilized with other types of cells in order to treat a whole range of diseases requiring endocrine replacement therapy.

Transplantation of islets of langerhans, including intracerebral or intrathecal transplantation, has been proposed to treat diabetes (Jansson, L., and S. Sandler, Transplantation Proceedings (1990), volume 22, pages 775-776; Tze et al, Transplantation (1986), volume 41, pages 531-534). However, the number of islets needed to cure diabetes in rodents is so large that the size of the graft usually exceeds the diffusion distance for oxygen (Jansson, L., and S. Sandler, Transplantation Proceedings (1990), volume 22, pages 775-776), and revascularization can lead to graft rejection (Menger, M.D., S. Jaeger, P. Walter, F. Hammersen, and K. Messmer, Transplantation Proceedings (1990), volume 22, pages 802-803). The diabetic state itself can also adversely affect islet transplantation (Warnock, G.L., N.M. Kneteman, and R.V. Rajotte, Transplantation Proceedings (1990), volume 22, pages 804-805). In addition, there is growing evidence that type I (insulin dependent) diabetes is an autoimmune disease. The immunogenicity of islet cells remains a major obstacle to the use of islet transplantation (Sun, A.M., Methods in Enzymology (1988), volume 137, page 576). Thus, graft rejection and autoimmune destruction of transplanted pancreatic islets are major problems (Fan, M., Z. Lum, X. Fu, L. Levesque, I. Tai and A. Sun, Diabetes (1990), volume 39, page 519).

Current attempts to ameliorate the effects of Parkinsonism by using adrenal cells or fetal substantia nigra cells transplanted directly into the brains of humans have produced transient improvements only. Moreover, the long term effects and possible auto-immune reactions to such direct intracerebral transplants is a continuing cause for concern.

The possibility of utilizing live tissue in an implantable device, comprised of a synthetic membrane, for the purpose of organ replacement was first established in the late 1970s (Galletti, P.M., Colloque Inserm (1989), volume 177, pages 3-12). Such immuno-isolated transplants must have a permeable membrane which allows the transport of nutrients and chemical messengers from the environment to the tissue and which allows the release of effector substances from that tissue into the appropriate body site. Some requirements of the membrane are described in Galletti, P.M., "The Concept of Bioartificial Endocrine Organs", Colloque Inserm (1989), volume 177, pages 3-12.

In general, two techniques have been utilized: microencapsulation and macroencapsulation. Microencapsulation involves encapsulating a cell or cell cluster with a permeable polymer gel with subsequent injection into the body. Macroencapsulation involves sealing cell suspensions into permeable tubular membranes and subsequently implanting the tubes into the body. Use of immuno-isolated transplants has been proposed to treat type I (insulin dependent) diabetes. Microencapsulation of islet cells has been used to treat diabetes in rats and humans (Fan, M., Z. Lum, X. Fu, L. Levesque, I. Tai and A. Sun, Diabetes (1990), volume 39, page 519; Wu, Z.G., Z.Q. Shi, Z.N. Lu, H. Yang, F.Y. Shi, X.R. Zheng, and A.M. Sun, Trans. Am. Soc. Artif. Intern. Organs (1989), volume 35, pages 736-738). However, disadvantages of microencapsulation and macroencapsulation include (1) biocompatibility of the artificial membrane, (2) fibrosis associated with tubes

which inhibit the entrance of nutrients and oxygen and the exit of products, thus compromising in vivo survival of the cells and preventing the device from being operable for a sufficient time, and (3) long diffusion distances associated with thick membranes or large tissue chambers.

The present invention lacks the disadvantages and shortcomings of the prior art and provides a spinal fluid driven device and method for treating diseases. One advantage of the present device is that it will successfully isolate cells from the problem of the abnormal microangiopathic environment and it makes it much easier to control the hyperglycemic state because of the lag between the blood sugar level and the spinal fluid level, which tends to be slower to respond to changes in blood sugar level, thus blunting the effects of sudden surges in blood sugar level.

Summary of the Invention

One of the objects of the present invention is to provide a spinal fluid driven artificial organ that can be utilized in treating disease such as diabetes. The device is constructed primarily of medical grade silicon rubber identical to that used in chronically implantable devices placed in subcutaneous regions of the body such as the Ommaya Reservoir and the Pudenz Hydrocephalus shunting device. Either allografts or xenografts will be introduced into a central chamber through which a one-way flow of cerebrospinal fluid will pass via two micropore filters. This arrangement enables the cerebrospinal fluid to function in three roles: (a) as a nutrient for the grafts, (b) as a source of chemical signals to the graft, and (c) as a fluid flow enabling transfer of the graft secretions to the host's body.

Brief Description of the Drawings

Figure 1 shows a top, cross-sectional view of the spinal fluid driven artificial organ with the cross-section taken at level I-I in Figure 1.

Figure 2 shows a side, cross-sectional view of the spinal fluid driven artificial organ with the cross-section taken at level II-II in Figure 1.

Figure 3A-3D shows three possible placements of the spinal fluid driven artificial organ in a patient depending on how the cerebrospinal fluid is caused to flow through the system. The device itself is always placed in a sub-cutaneous location. Figure 3A shows spinal-peritoneal system placement. Figure 3B and 3C show ventriculo-cisternal system placement. Figure 3D shows spinal-vascular system placement.

Detailed Description of the Invention

The spinal fluid driven artificial organ 10 is an implantable neurosurgical device which enables the transfer of cerebrospinal fluid (CSF) from the spinal CSF space to the artificial organ and then into the peritoneal space or other absorptive space, such as blood vessels, or back into cerebrospinal fluid.

With reference to figures 1 and 2, there is shown the spinal fluid driven artificial organ 10. The tripartite chamber "A" has three sections (1, 2, 3). Micropore filter "B" separates chamber section 1 from chamber section 2. Micropore filter "C" separates chamber section 2 from chamber section 3. CSF enters chamber section 1 via an inlet tube (T1) and a one way valve (V1). Micropore filter "B" allows entry of CSF into chamber section 2 but does not allow exit of any cells from chamber section 2 into chamber section 1. Micropore filter "C" allows free passage of CSF from chamber section 2 into chamber section 3 and prevents any cells in chamber section 2 from entering chamber section 3. The CSF flow exits chamber section 3 via a one way valve (V2) and an outlet tube (T2). The

outlet tube (T2) delivers the CSF to the desired location.

Depending on the disease indication which is to be treated, the placement of the device and its input/output catheters (tubes) can be any one of three locations: ventriculo-spinal for diseases requiring hormonal substances to be delivered primarily to the central nervous system, spinal-peritoneal or spinal-vascular for diseases requiring hormonal substances to be delivered to other body systems. Figure 3A depicts the spinal-peritoneal placement indicated for the delivery of insulin from islet cells in the device chamber in cases of insulin dependent diabetics. Figures 3B and 3C depict the ventriculo-cisternal placement for delivery of dopamine from substantia nigra grafts to the central nervous system. Figure 3D depicts the spinal-vascular placement for indications similar to that needing the spinal-peritoneal (3A) placement. In any and all of these three types of placement, the artificial organ chamber part will always be in a subcutaneous location, only the input and output tubes being differently placed as shown in figure 3A.

Central chamber section 2 contains the desired transplanted cells 7. The desired cells are loaded into chamber section 2 by subcutaneous injection through the self-sealing, repeatedly punctureable dome 6 of chamber "A". The CSF flowing from chamber section 1 into chamber section 2 nourishes the cells and provides a signal to the cells to produce products (e.g., to make insulin). The CSF flowing through chamber section 2 provides the motive power to carry secreted products from the cells through micropore filter "C" into chamber section 3.

Because the CSF flow is only in the one direction (designated F) and because of the motor force provided by the CSF flow through, cellular material from other sites in the body cannot migrate against the CSF flow to enter organ chamber "A". Thus, there will be no

threat to the immunological isolation of the cells in chamber section 2. The desired cells in chamber section 2 can be easily placed, replenished or removed for replacement by fresh transplants as needed by simple subcutaneous injection through the dome of chamber "A". The dome 6 is easily identified by location of two ridges 8, marking the locations of the two micropore filters "B" and "C" (see figure 2), under the overlying skin. The quality of the hormonal content of CSF reaching chamber section 3 can also be easily assayed, through the use of a syringe and suitable hypodermic needle, by subcutaneous sampling of the fluid in chamber section 3. Artificial organ 10 is secured to fascia (not shown) through use of flanges 5 preferably formed by dacron or silicon.

The desired cells in chamber section 2 may be insulin secreting pancreatic islet cells. The cells may be from any source (e.g., human cadavers, pigs, etc.). The cells may be from a cryopreserved source. Other types of cells which may be used will be, for example, fetal substantia nigra cells for treating patients with Parkinsonism or growth hormone secreting cells for treating patients with growth deficiencies.

All of the above cells may be isolated and treated according to known methods, e.g., Scharp, D.W., et al., Diabetes (1990), volume 39, pages 515-6; Z. Lum, X. Fu, L. Levesque, I. Tai and A. Sun, Diabetes (1990), volume 39, page 519); Sun, A.M., Methods in Enzymology (1988), volume 137, page 576; and Warnock, G.L., D.K. Ellis, and R.V. Rajotte, Transplantation (1988), page 957.

Chamber "A" is generally made of medical grade silicon rubber reinforced at suitable sites with dacron or teflon mesh. All materials to be used are available and have been used for chronic implanted devices for many years in patients.

The inlet tube (T1) and outlet tube (T2) are approximately 1 mm in diameter. These tubes are generally made of medical grade silicon rubber.

Micropore filters "B" and "C" have pores of about 1-5 μ in diameter and are commercially available. The filters are impermeable to cells and effector molecules of the immune system, thus providing total protection to transplanted islets against rejection. The filter does allow transport of small molecular nutrients, hormones and metabolites.

The desired location for delivery of the CSF by the outlet tube (T2) may be the peritoneal space when insulin secreting pancreatic islet cells are placed in chamber section 2, thus enabling physiological control of diabetes mellitus (Type I). Other systemic hormonal deficiency diseases may be similarly treated when the appropriate cells are utilized in chamber section 2 (e.g., substantia nigra cells which secrete dopamine). The output from the outlet tube (T2) may be directed back into the CSF space if a central nervous system deficiency state (e.g., Parkinson's Disease) is to be corrected by the appropriate delivery of a neurotransmitting hormone or trophic factor produced by the appropriate cells implanted in chamber section 2.

Figure 3A shows a spino-peritoneal placement of Artificial Organ 10 in, for example, a patient with Diabetes Mellitus Type I. In Figure 3A the reference numbers listed below depict the following:

11--CSF containing spinal thecal sac

12--extension of outlet tube T2 in peritoneal cavity

13--chamber A positioned below skin in lower abdominal quadrant

14--spinal intrathecal inlet tube T1 enabling CSF flow to Artificial Organ chamber.

Figure 3B and 3C show Artificial Organ 10 in a ventriculo-cisternal system placement. In Figure 3B reference numbers depict the following:

15--cerebral ventricular cavity with CSF

16--flushing valve (one way)

17--subcateneous outflow CSF catheter

Figure 3C shows a cross-section of the body at a L3/4 level. As shown in Figure 3C, catheter 17 provides an inlet tube for the CSF flowing into artificial organ 10. The below listed reference numbers depict the following in Figure 3C:

18--front of lower abdomen (cross-section)

19--back of person

20--spine of person

21--spina CSF space

Figure 3D shows a cross-section of the abdomen and a spinal-vascular system placement of the artificial organ 10. The below listed reference numbers depict the following in Figure 3D:

22--large intra abdominal vein (e.g., portal vein)

23--intravascular catheter with slit valve at tip

24--intra abdominal outflow catheter entering vein

25--subcutaneous CSF inflow catheter.

Further variations and modifications of the invention will become apparent to those skilled in the art from the foregoing and are intended to be encompassed by the claims appended hereto.

What is claimed:

1. A passive spinal fluid driven artificial organ device for delivering a biologically active product to a human or mammal, comprising

an organ chamber divided into at least three sections with at least two filters to separate said sections from each other,

a first section of said organ chamber adapted to receive at least one type of product-secreting cells,

a second section of said organ chamber having an inlet tube and a one way valve for passage of spinal fluid into said second section,

and a third section of said organ chamber having an outlet tube and a one way valve for outward flow of said spinal fluid and the products of said product-secreting cells,

whereby said spinal fluid entering and flowing through said second, first and third sections, respectively, acts as a nutrient medium for said product-secreting cells and causes the passage of said products of said product-secreting cells out of said organ device, and wherein said filters allow unimpeded flow of said spinal fluid while retaining said cells in said first section.

2. The device according to claim 1, wherein at least one section is adapted to receive cells.

3. The device according to claim 2, wherein said cells are pancreatic islet cells.

4. The device according to claim 1, further comprising an inlet tube and one way valve connected to one of said sections.

5. The device according to claim 1, further comprising an outlet tube and one way valve connected to one of said sections.

6. The device according to claim 1, wherein the exterior surface of said device has a ridge substantially defining the location of said first section within said organ chamber.

7. The device according to claim 1, wherein said filters have about 1-5 μ pores.

8. The device according to claim 2 adapted to receive spinal fluid which flows through said organ chamber and acts as nutrient medium and as motive force to transfer cell secretions from said cells.

9. The device according to claim 8, wherein said body fluid is cerebrospinal fluid.

10. The device according to claim 2, wherein said cells are substantia nigra cells.

11. A method for treating disease in humans and mammals, comprising utilizing the device according to claim 1.

12. The method according to claim 11, wherein said disease is diabetes mellitus.

13. The method according to claim 11, wherein said disease is Parkinsonism.

14. The device according to claim 1, wherein said filters are adapted to allow spinal fluid to flow in only one direction.

15. The method according to claim 11, wherein said device is placed subcutaneously in said human or said mammal.

16. A spinal fluid driven artificial organ device for delivering a biologically active product to a human or mammal, the device comprising an organ chamber divided into at least three sections with at least two filters to separate said sections from each other, said organ chamber adapted to receive at least one product-secreting cell, said filters adapted to be held in contact with a source of spinal fluid for introducing spinal fluid into said organ chamber; and pumping means providing solely physiologically generated spinal fluid causing transportation of a secreted product from said organ chamber to a selected region in said human or mammal, said pumping means comprising spinal fluid which flows through said organ chamber and acts as nutrient medium and as a motive force to transfer cell products from said cells.

17. The device according to claim 16, wherein said pumping means consists essentially of spinal fluid.

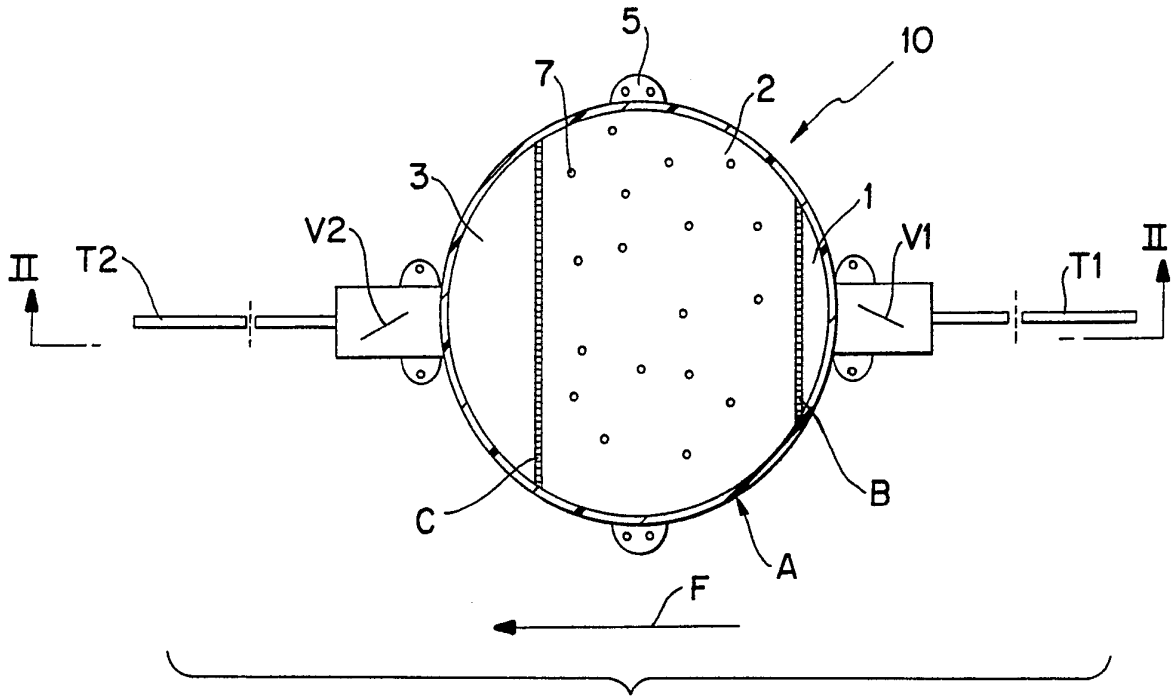

FIG. 1

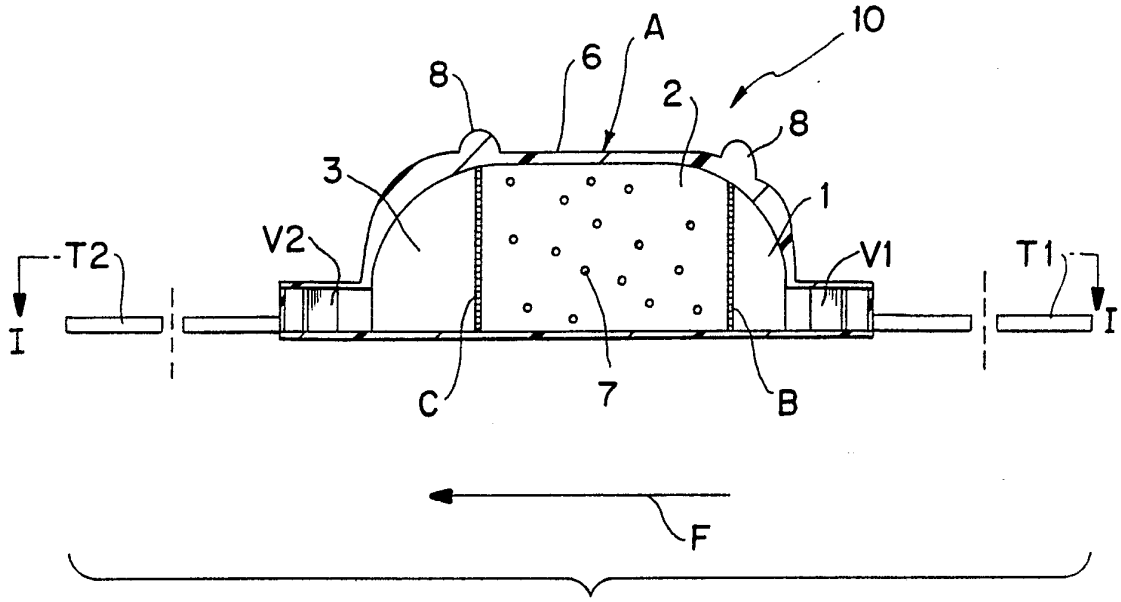

FIG. 2

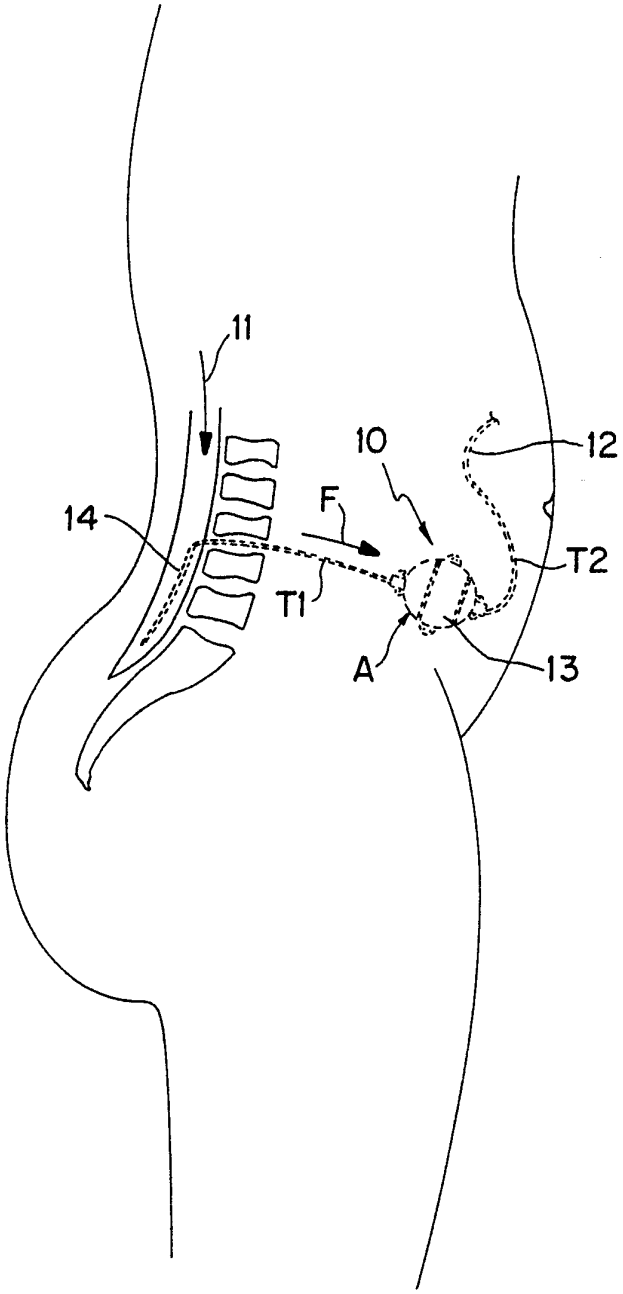

FIG. 3A

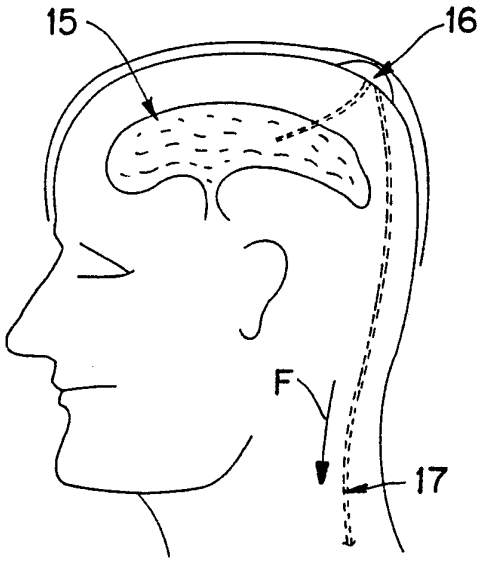

FIG. 3B

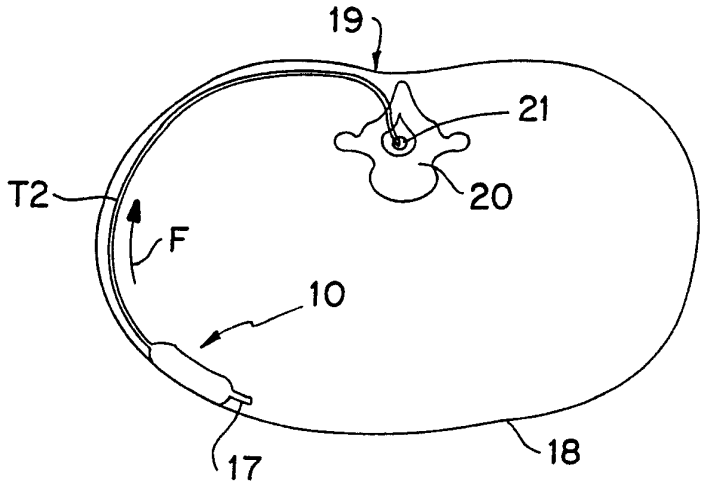

FIG. 3C

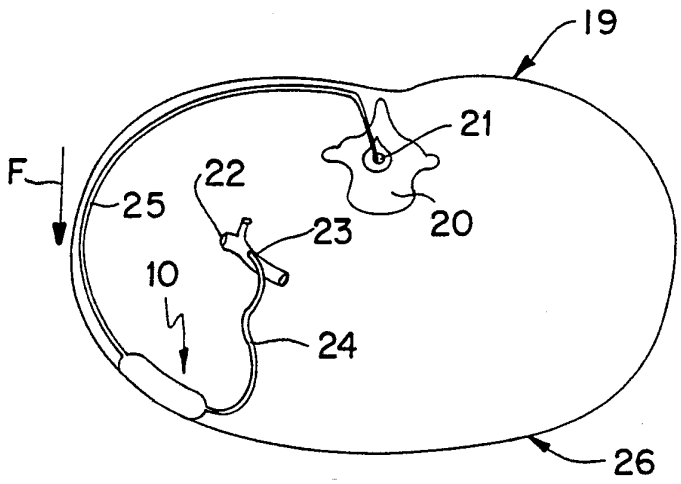

FIG. 3D

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/00947

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5) : A61F 2/04

U.S. Cl.: 623/12, 604/890.1, 604/8

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S. Cl.	435/284, 285,286 604/4-6,8-10,390.1,891.1,892.1 623/12

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4,201,845 (FEDER et al) 06 MAY 1980 Note fiber layer and micro-phorous filters 40,41 in figure 4.	1-2 and 16-17
A	US, A, 4,559,299 (ROTMAN) 17 DECEMBER 1985 Note valves 44,46 and the seperation of chambers with membranes 32 (figure 2a).	1-8 and 16-17
A	US, A, 5,011,472 (AEBISCHER et al) 30 APRIL 1991 Note cell resorvoir 40 and semipermeable membranes 36 and 38 in figure 3 A.	16-17
A	US, A, 0398983, (FISCHER, K.H. et al) Note the plurality of chamber sections and the plurality of semipermeable membranes 11 in figure 7.	16-17

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13 APRIL 1992	23 JUN 1992
International Searching Authority	**Signature of Authorized Officer**
ISA/US	DAVID H. WILLSE

Form PCT/ISA/210 (second sheet) (Rev.11-87)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X,P	EP, A,	0421380,	(KANEGAFUCHI KABUSHIKI KAGAKU KOGYO KAISHA) 10 APRIL 1991 Note filters 4 and 5, inlet and outlet 2 in figure 1.	16-17

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . . . . . , because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.