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(71)(72) Applicants and Inventors: ARNOLD, Francis, William [US/GB]; 136 Sandy Lane, Chorlton, Manchester M21 2TZ (GB). SUTTON, Malcolm [GB/GB]; 664 Wilmslow Road, Manchester (GB). DRAYSON, Mark [GB/GB]; 20 Brownsville Road, Heaton Moor, Stockport SK4 4PR (GB).

(74) Agent: MASSEY, Alexander; Marks & Clerk, Suite 301, Sunlight House, Quay Street, Manchester M3 3JY (GB).

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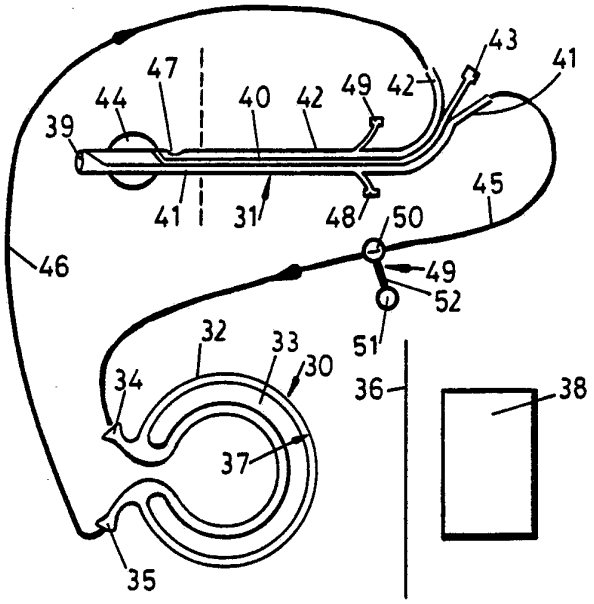
(54) Title: DEVICE FOR USE IN THE TREATMENT OF LYMPHOCYTES



(57) Abstract

An implantation device for use in the in-vivo destruction of thoracic duct lymphocytes has in adjacent but separate relationship a passage through which lymph to be treated can flow and an irradiation source capable of destroying lymphocytes. The irradiation source may be either a beta emitting radio isotope or an ultraviolet light source. A cannula device for diverting untreated lymph from, and returning treated lymph to, the thoracic duct is provided for communication with the treatment device.

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DEVICE FOR USE IN THE TREATMENT OF LYMPHOCYTES

This invention relates to a device for use in the treatment of cells circulating in lymph or other body fluids and especially but not exclusively for use in the treatment of thoracic duct lymphocytes.

For convenience reference will be made in the description and in the claims solely to "thoracic duct lymphocytes" but such references are not to construed limitatively in that cells other than lymphocytes may be treated in accordance with the present invention and/or in that anatomical channels other than the thoracic duct may be fitted with the device according to the invention.

The device of the present invention is particularly for use in destroying thoracic duct lymphocytes.

Lymphocytes are cells which are well known to be critical to the body's immune reactions. Approximately 70% of newly generated lymphocytes traverse the thoracic duct in transit to the blood stream.

Established treatments of lymphocytes include drugs, lymphoheresis and external beam irradiation, all of which produce potentially unacceptable side effects, require prolonged hospitalisation and may be, or may become, ineffective. The present invention is concerned particularly with irradiation treatment.

It is known that whole body irradiation and total nodal irradiation are currently being used beneficially in non-malignant conditions in which auto-immunity appears to be a feature of the disease process. Examples of diseases being treated in this

way are rheumatoid arthritis, cystemix lupus erythematosus, polymyositus, and more recently disseminated sclerosis. A common feature of these disease conditions is that removal of lymphocytes from thoracic duct lymph often results in rapid (within days) clinical improvement, and this is also true for acute episodes of rejection of transplanted organs.

The removal of thoracic duct lymphocytes involves drainage of the thoracic duct, and such drainage is difficult, labour intensive, and expensive, and cannot be considered for routine use particularly in the treatment of rheumatoid arthritis and disseminated sclerosis which are relatively common diseases. Wide field irradiation (whole body and/or nodal) of large numbers of patients with non-malignant disease is undesirable and would not be employed if an effective alternative treatment was available.

It is well known to those skilled in the art of medicine that the lymphocyte has the almost unique ability among human cells to undergo rapid interphase death following irradiation (ultraviolet irradiation for example); it is inherently more radio-sensitive than most other normal cells; and, in patients with rheumatoid arthritis at least, circulating lymphocytes are strikingly more sensitive than even normal lymphocytes.

It is accordingly an object of the present invention to provide a device which offers the aforesaid effective alternative treatment, i.e. replacement of wide field irradiation, and which more particularly serves for the in-vivo destruction of thoracic duct lymphocytes.

For convenience and simplicity the device is

hereinafter and in the claims referred to as "treatment device".

According to the present invention, therefore, there is provided a treatment device comprising a hollow body adapted for implantation in the thoracic duct and defining a passage through which thoracic duct lymph is adapted to flow, and an irradiation source capable of destroying lymphocytes located adjacent to but separate from the lymph flow passage.

The irradiation source may be a beta emitting radio isotope housed within a compartment surrounding and enclosing the lymph flow passage.

Alternatively the beta emitting radio isotope may be housed within a compartment subtantially parallel with the lymph flow passage. In this instance, the hollow body may be in the form of a tube divided internally by a membrane to provide the lymph flow passage separate from the isotope containing compartment.

Preferably, the outer wall of the isotope containing compartment of the tubular body at least is radiation shielded.

Preferably the isotope containing compartment communicates with a small volume reservoir into which isotope, in liquid form, can be injected through an injection port for flushing into the isotope containing compartment.

This small volume reservoir may also provide an exit means for extraction of the liquid isotope from the compartment.

The reservoir and isotope-containing compartment are preferably connected by a valve adapted to permit low pressure injection of liquid isotope into the compartment but requiring high pressure suction to extract liquid isotope from the compartment into the

reservoir.

It is preferred that the lymph flow passage of the device is made of, or lined with, non-thrombogenic material.

The beta emitting radio isotope used in the device to permit intermittent operation of the device is preferably either beta emitting radio isotope of short half-life, or beta emitting radio isotope of long half-life, the isotope containing compartment of the device being adapted to permit removal of the isotope in the latter instance.

The irradiation source may alternatively be an ultraviolet source.

Preferably a radio frequency power supply separate from the treatment device is provided to induce ultraviolet emissions from the ultraviolet light source.

Preferably, the ultraviolet light tube is provided with a reflective surface at its surface remote from the radio frequency power supply to minimise energy losses.

The ultraviolet light source tube is preferably C-shaped and may, inter alia, be constructed of quartz and contain mercury vapour.

The treatment device is preferably in communication with a cannula device for diversion of lymph from the thoracic duct to the treatment device and thence back to the thoracic duct or central venous system, the cannula device being provided with means for fixing the cannula device in position with the thoracic duct.

Preferably the fixing means is an inflation device such, for example, as an inflatable balloon.

Preferably the cannula device has three separate tubular passages, one for use in inflating the balloon, a second for passage of untreated lymph from the thoracic duct to the treatment device, and a third for passage of treated lymph back to the thoracic duct.

Preferably, the second and third tubular passages have ports normally closed by valves for use in clearing any blockages within the tubular passages and for taking lymph samples if desired or required.

Preferably the second passage is connected to the inlet of the lymph flow passage of the treatment device by a tube which is at least partly flexible in nature, a pump being connected to the tube to ensure maintenance of lymph flow and being adapted to be implanted in the chest wall.

Preferably the pump comprises a pair of balloons joined by a communicating tube and containing fluid, for example water, with one balloon surrounding the flexible tube and the other being disposed within the chest wall of a patient so that compression of the other balloon by chest wall movements causes repeated compression and expansion of the flexible tube thereby pumping lymph along the flexible tube to the treatment device, flow in the opposite direction being prevented by an anatomical valve upstream in the thoracic duct in terms of the direction of lymph flow.

Preferably all surfaces of the treatment device and the cannula device which are contactible by lymph are non-thrombogenic in nature.

The treatment and cannula devices are preferably wholly constructed of biologically compatible materials.

The treatment and cannula devices are preferably adapted for subcutaneous implantation but

may be reside externally of the patient's body or be only partially implanted.

Embodiments of the present invention will now be described, by way of example, with reference to the accompanying drawings, in which:-

Fig. 1 is a diagrammatic sectional view of a first embodiment of treatment device;

Fig. 2 is a view similar to Fig. 1 of a second embodiment of treatment device;

Fig. 3 is a diagrammatic view of a third embodiment of treatment device in combination with a cannula device which is used also with the treatment devices of the first and second embodiments; and

Fig. 4 is a detail view of the pump.

Referring to Fig. 1 the treatment device comprises a passage through which lymph can flow the passage being designated 10 and having an inlet 11 and an outlet 12. The lymph flow passage 10 is enclosed within a compartment 13 containing a beta emitting radio isotope generally indicated at 14.

The beta emitting radio isotope 14 is preferably in liquid form and the compartment 13 is connected to a small volume reservoir 15 having an injection port 16 which is connected to the compartment 13 by a small diameter flexible tube 17. The tube 17 contains a valve 18 which is of a nature whereof it is adapted to open upon low pressure injection of liquid beta emitting radio isotope through the patient's skin 19 and the injection port 16 into the reservoir 15 from where it is flushed along the tube 17 into the compartment 13. The valve 18 is also capable of opening to permit flow of liquid beta emitting radio isotope 14 from the compartment 13 into the reservoir only by the application of high pressure suction to the injection port 16.

The treatment device, save for the area around the injection port 16, is enclosed in low molecular weight shielding 20, such for example as aluminium shielding.

Referring now to Fig. 2, the treatment device comprises a fusiform hollow tubular body 21 for implanation in the terminal thoracic duct of a patient, the tubular body 21 having at opposed ends an inlet 22 and an outlet 23 for, respectively, ingress into, and egress out, of the tubular body 21 of the patient's thoracic duct lymph.

The tubular body 21 is divided internally by a thin flexible membrane 24 to define, in separated relationship, a passage 25 for flow of lymph through the tubular body 21 and a compartment 26 within which is disposed beta emitting radio isotope 27.

The compartment 26 communicates via tubing 28 incorporating a valve with a small volume reservoir (not shown) but as described with reference to Fig. 1, which reservoir is accessible through the subcutaneous tissues of the patient's neck when the treatment device is implanted. As aforesaid, liquid beta emitting radio isotope can be injected through the patent's skin into this reservoir and be flushed therefrom through the tubing 28 into the compartment 26, or sucked from the latter into the reservoir.

The wall of the tubular body 21 is radiation shielded as indicated at 29.

The lymph flow passage 15 is either made of, or is lined with, non-thrombogenic material.

Reference is now made to Fig. 3 which shows a further embodiment of treatment device generally indicated at 30 and a cannula device generally indicated at 31.

It is to be clearly understood that this

cannula device would also be used with the treatment devices of Figs. 1 and 2.

The treatment device comprises a C-shaped a body defining a flow passage 32 housing a C-shaped ultraviolet source tube 33, the C-shaped passage 32 having an inlet 34 for untreated lymph from the patient's thoracic duct and an outlet 35 for treated lymph.

The patient's skin is indicated by the reference 36 and the surface of the ultraviolet source tube 33 designated 37 is made reflective to minimize energy losses.

Ultraviolet emission from the ultraviolet source tube 11 is induced by a separate radio-frequency power supply 38 external of the patient's body. This power supply 38 is of a capacity to evoke discharge within the ultraviolet source tube 33 at levels sufficient to destroyed lymphocytes within the passage 32. The power supply 38 may be switched on or off to achieve the desired level of immunodepression or may be used intermittently to increase the patient's mobility.

The cannula device 31 is open at one end as indicated at 39 for passage thereinto of lymph from a patient's thoracic duct and it contains three parallel passages 40, 41 and 42, all separate one from another.

The passage 40 has a valve controlled inlet 43 connected to an inflatable balloon 44 disposed adjacent the lymph inlet end 39 of the cannula device 31. The balloon 44 can be inflated by the introduction of water through the valve control inlet 43 and along the passage 40 for the purpose of fixing the cannula device 31 within the patient's thoracic duct, the cannula device 31 being inserted into the

thoracic duct through a hole in the side thereof.

The passage 41 which communicates with the lymph inlet opening 39 is connected by a tube 45 to the inlet 34 of the treatment device 30.

The third passage 42 is connected by a tube 46 to the outlet 35 of the treatment device 30 and the passage 42 is open as indicated at 47 to the thoracic duct of the patient.

The passages 41 and 42 are respectively provided with valve controlled ports 48 and 49 which may be used to clear any blockages in the passages 41, 42, or to permit the extraction of samples of untreated lymph from passage 41 and treated lymph from passage 42.

When the cannula device 31 is inserted into the thoracic duct by recognised surgical techniques and the balloon 44 inflated to fix the cannula device 31 in position, lymph enters the passage 41 through the inlet 39 and passes from there through inlet 34 into the passage 32 of the treatment device 30 where the lymph is subjected to ultraviolet radiation from the ultraviolet source tube 33 at levels which ensure destruction of all lymphocytes within the treatment device 30. The treated lymph then returns via the tube 46 into passage 42 of the cannula device 31 and out through the opening 47 back into the thoracic duct.

A pump generally indicated at 49 is associated with the connecting tube 45 between the passage 41 of the cannula device and the inlet 34 of the treatment device 30. The connecting tube 45 is resilient in nature at least at its length with which the pump 49 is operatively associated.

This pump 49 comprises two balloons 50 and 51 connected by a tube 52 and containing water.

The balloon 51 of the pump 49 at least is disposed within the patient's chest wall, and due to movements of the chest wall, the water is caused to flow back and forth between the balloon 51 and 50 thus compressing and expanding continuously the resilient connecting tube 45, thereby effecting a pumping action on the lymph flowing through the tube 45. This flow is unidirectional since flow in the other direction is resisted by a one way anatomical valve in the patient's thoracic duct system.

The treatment devices, according to this invention, are characterised by the following features taken either singly or in selected or total combination:-

1) The device is intended as a permanent or semi-permanent implant through which will flow the entire contents of the terminal portions of the thoracic duct of a patient.
2) The interior of the device contains either a pure beta emitting radio isotope or an ultraviolet source tube throughout most of its length.
3) The physical characteristics of the selected isotope or the levels of ultraviolet radiation are such that the lymphocytes are lethally irradiated in a single pass through the device.
4) The device, where an isotope is used, is shielded to protect surrounding tissues from beta irradiation which has finite penetration.
5) The device, where an isotope is used, is made from material of such atomic number as to generate little or no bremstrahlung photon irradiation of the surrounding tissues.
6) The device of Fig. 1 or Fig. 2 is capable of intermittent operation either by being charged

with a beta emitting radio isotope of short half-life, or of beta emitting radio isotope of long half-life with provision, in the latter case, of removal of the isotope from the device.

7) The isotope selected for clinical use in the device of Fig. 1 or Fig. 2 does not participate in human metabolic processes and, in the event of leakage of isotope from the device into the patient's body fluid circulation, is rapidly excreted by the kidneys.

8) The device of Fig. 3, by control of its power supply, may be switched on or off to achieve the desired level of immunodepression, or it may be used intermittently to increase a patient's mobility.

CLAIMS

1. A treatment device comprising a hollow body adapted for implantation in the thoracic duct and defining a passage through which thoracic duct lymph is adapted to flow, and an irradiation source capable of destroying lymphocytes located adjacent to but separate from the lymph flow passage.

2. A device as claimed in claim 1, in which the irradiation source is a beta emitting radio isotope housed within a compartment surrounding and enclosing the lymph flow passage.

3. A device as claimed in claim 1, in which the beta emitting radio isotope is housed within a compartment subtantially parallel with the lymph flow passage.

4. A device as claimed in claim 3, in which the hollow body is in the form of a tube divided internally by a membrane to provide the lymph flow passage separate from the isotope containing compartment.

5. A device as claimed in any one of claims 1 to 4, in which the wall of the isotope containing compartment of the tubular body at least is radiation shielded.

6. A device as claimed in any one of claims 1 to 5, in which the isotope containing compartment communicates with a small volume reservoir into which isotope, in liquid form, can be injected through an injection port for flushing into the isotope containing compartment.

7. A device as claimed in claim 6, in which the small volume reservoir also provides an exit means for extraction of the liquid isotope from the compartment.

8. A device as claimed in claim 7, in which the reservoir and isotope-containing compartment are connected by a valve adapted to permit low pressure injection of liquid isotope into the compartment but requiring high pressure suction to extract liquid isotope from the compartment enter the reservoir.

9. A device as claimed in any one of claims 1 to 8, in which the lymph flow passage of the device is made of, or lined with, non- thrombogenic material.

10. A device as claimed in any one of claims 1 to 9, in which the beta emitting radio isotope used in the device to permit intermittent operation of the device is either beta emitting radio isotope of short half-life, or beta emitting radio isotope of long half-life, the isotope containing compartment of the device being adapted to permit removal of the isotope in the latter instance.

11. A device as claimed in claim 1, in which the irradiation source is ultraviolet in nature.

12. A device as claimed in claim 11, in which the ultraviolet source is in the form of an ultraviolet light tube contained within the lymph flow passage.

13. A device as claimed in claims 11 or 12, comprising a radio frequency power supply separate from the treatment device to induce ultraviolet emissions from the ultraviolet light source.

14. A device as claimed in claim 13, in which the ultraviolet light tube is provided with a reflective surface at its surface remote from the radio frequency power supply to minimise energy losses.

15. A device as claimed in any one of claims 12 to 14 in which the ultraviolet light source type is C-shaped and is constructed of quartz and contains

mercury vapour.

16. A treatment device as claimed in any one of claims 1 to 15 in combination and in communication with a cannula device for diversion of lymph from the thoracic duct to the treatment device and thence back to the thoracic duct, the cannula device being provided with means for fixing the cannula device in position with the thoracic duct.

17. The combination as claimed in claim 16, in which the cannula device fixing means is an inflation device such, for example, as an inflatable balloon.

18. The combination as claimed in claim 17, in which the cannula device has three separate tubular passages, one for use in inflating the balloon, a second for passage of untreated lymph from the thoracic duct to the treatment device, and a third for passage of treated lymph back to the thoracic duct.

19. The combination as claimed in claim 18, in which the second and third tubular passages have ports normally closed by valves for use in clearing any blockages within the tubular passages and for taking lymph samples if desired or required.

20. The combination as claimed, in claim 18 or 19 in which the second passage is connected to the inlet of the lymph flow passage of the treatment device by a tube which is at least partly flexible in nature, a pump being connected to the tube to ensure maintenance of lymph flow and being adapted to the implanted in the chest wall.

21. The combination as claimed, in claim 20 in which the pump comprises a pair of balloons joined by a communicating tube and containing fluid, for example water, with one balloon surrounding the

flexible tube and the other being disposed within the chest wall of a patient so that compression of the other balloon by chest wall movements causes repeated compression and expansion of the flexible tube thereby pumping lymph along the flexible tube to the treatment device, flow in the opposite direction being prevent by an anatomical valve upstream of the thoracic duct in terms of the direction of lymph flow.

22. The combination as claimed in any one of claims 16 to 21, in which all surfaces of the treatment device and the cannula device which are contactible by lymph are non-thrombogenic in nature.

23. The combination as claimed in any one of claims 16 to 22, in which the treatment and cannula devices are wholly constructed of biologically compatible materials.

24. The combination as claimed in any one of claims 16 to 23, in which the treatment and cannula devices are adapted for subcutaneous implantation but may be reside externally of the patient's body or be only partially implanted.

25. A treatment device, substantially as hereinbefore described with reference to Fig. 1 or Fig. 2 or Fig. 3 and 4 of the accompanying drawings.

26. A cannula device for diversion of lymph from the thoracic duct to an irradiating treatment device and thence back to the thoracic duct, the cannula device being provided with means for fixing the cannula device in position with the thoracic duct.

27. A device as claimed in claim 26, in which the fixing means is an inflation device such, for example, as an inflatable balloon.

28. A device as claimed in claim 27, comprising three separate tubular passages, one for use in

inflating the balloon, a second for passage of untreated lymph from the thoracic duct to the irradiating treatment device, and a third for passage of treated lymph back to the thoracic duct.

29. A device as claimed in claim 28, in which the second and third tubular passages have ports normally closed by valves for use in clearing any blockages within the tubular passages and for taking lymph samples if desired or required.

30. A pump for maintaining flow of a body fluid, such, for example as lymph, through a flexible tube, the pump being at least partly implanted in a patient's chest and being operated by chest wall movements.

31. A pump as claimed in claim 30, comprising a pair of balloons joined by a communicating tube and containing fluid, for example water, with one balloon surrounding the flexible tube and the other being disposed within the chest wall of a patient so that compression of the other balloon by chest wall movements causes repeated compression and expansion of the flexible tube thereby pumping lymph along the flexible tube to the treatment device, flow in the opposite direction being prevent by an anatomical valve upstream of the thoracic duct in terms of the direction of lymph flow.

32. The use of a treatment device as claimed in any one of claims 1 to 25 for destroying, or controllably reducing the number of, lymphocytes in a circulating flow of lymph.

33. The use of a treatment device as claimed in any one claims 1 to 25 in treating auto-immune disorders, in preventing transplant rejection, and/or in treating other clinical and/or medical conditions in which the need for lymphocyte depletion is

diagnosed or indicated.

34. The use of a treatment device as claimed in any one of claims 1 to 25 in experiments in animal physiology, pathology and/or immunology.

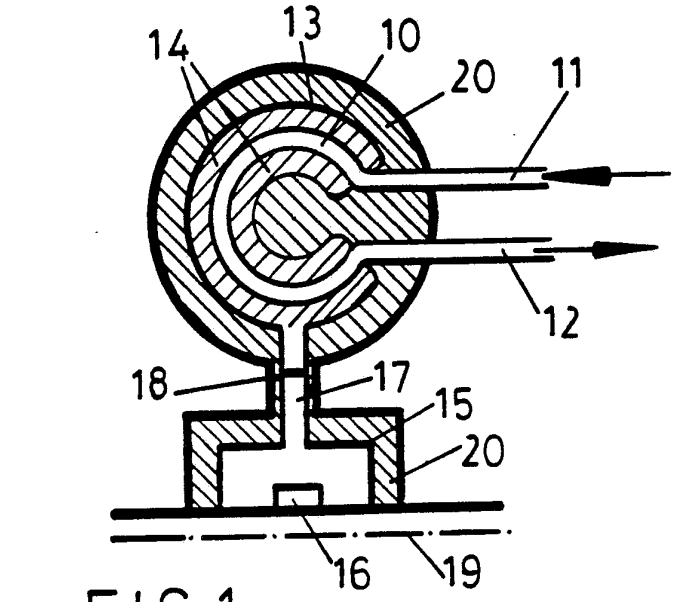

FIG.1

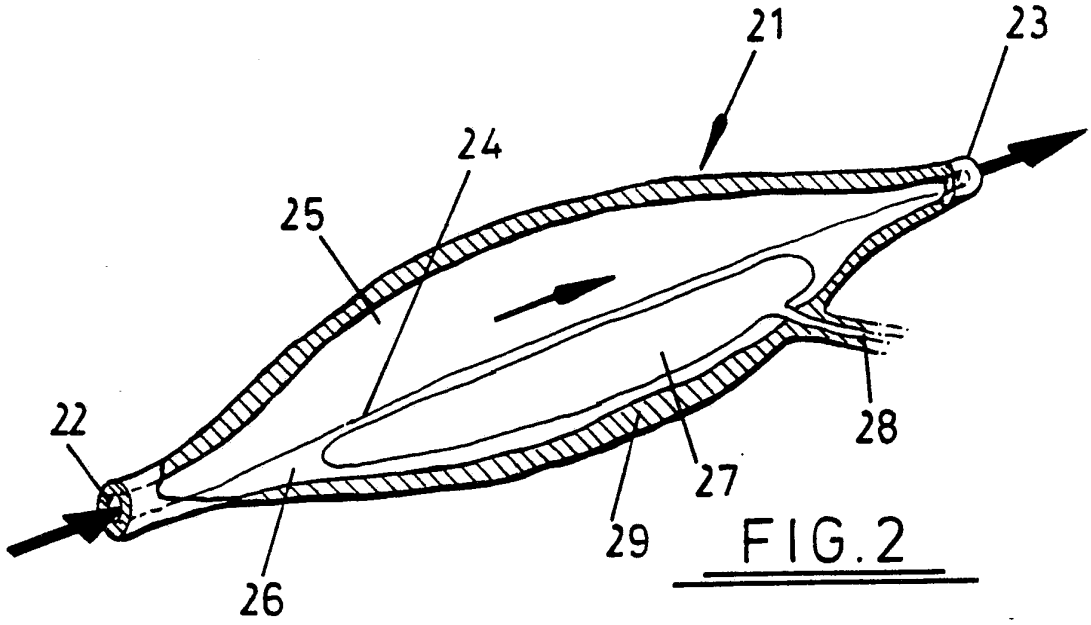

FIG.2

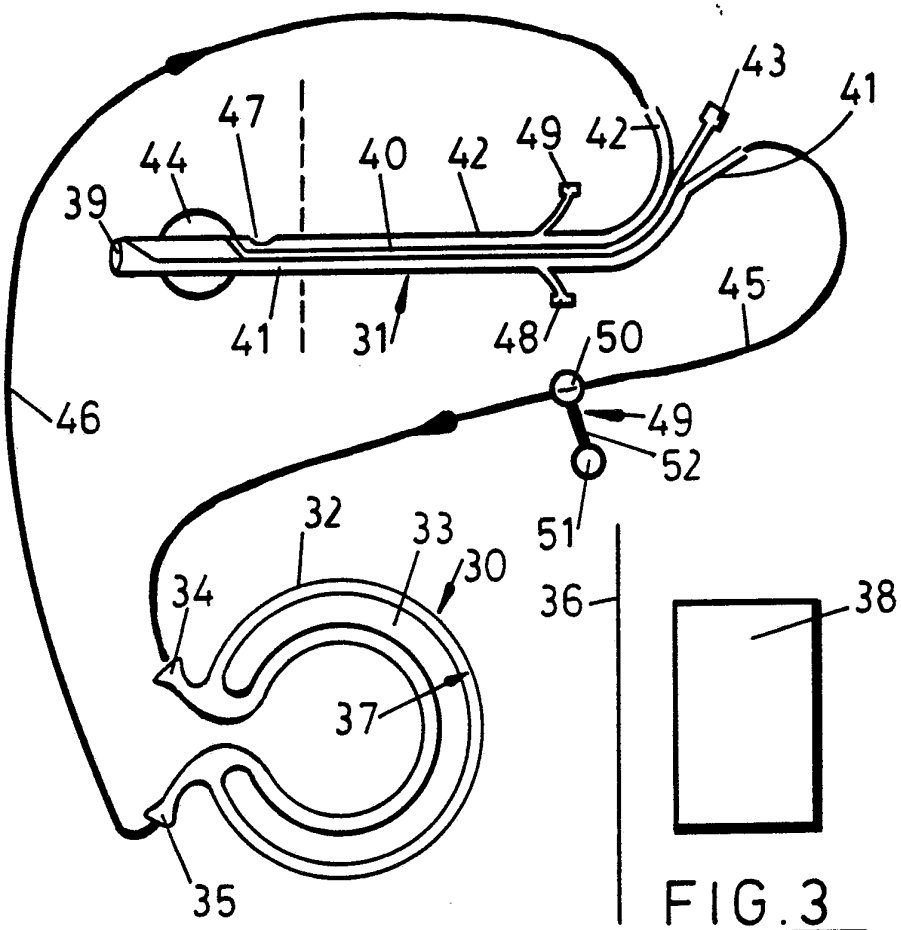
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FIG. 3

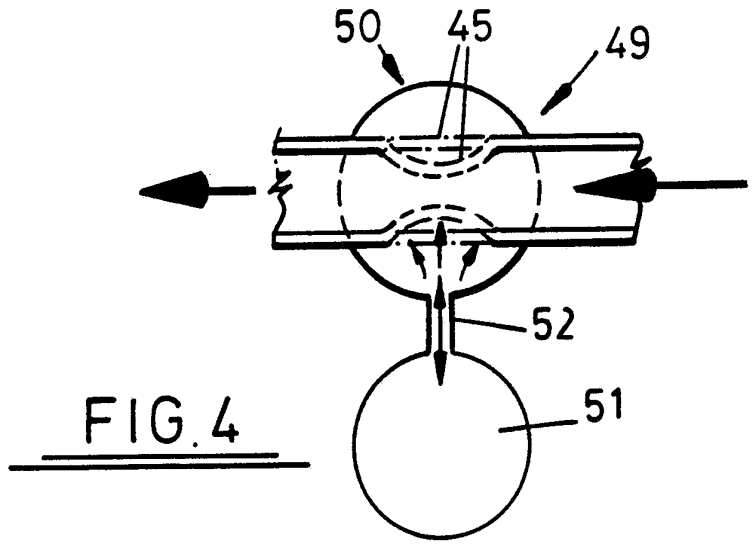
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FIG. 4

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 88/00951

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

IPC4: A 61 N 5/06, A 61 M 1/36, A 61 M 25/00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC4	A 61 N, A 61 M

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 [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	GB, A, 2100143 (RICHARD LESLIE EDELSON) 22 December 1982, see abstract --	1,2
Y	EP, A1, 0138489 (EXTRACORPOREAL MEDICAL SPECIALITES INC) 24 April 1985, see abstract --	1,2
Y	EP, A1, 0101890 (AIGNER,KARL, DR.) 7 March 1984, see the whole document --	1,2
X	US, A, 3211150 (J.W. FODERICK) 12 October 1965, see the whole document --	30

[10] Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
31st January 1989	13 FEB 1989
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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A	GB, A, 2200020 (ANDREW GUNN ET AL) 20 July 1988, see the whole document --	1-34
A	EP, A1, 0218275 (FIJNEMAN, M J A J) 15 April 1987, see the whole document --	1-34
A	EP, A1, 0240149 (MCNEILAB, INC) 7 October 1987, see the whole document --	1-34
A	US, A, 4512762 (SPEARS) 23 April 1985, see the whole document --	1-34

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 88/00951

SA 25110

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 12/01/89
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		AU-D-	23459/84	18/06/84
		EP-A-	0126152	28/11/84
		JP-T-	60500845	06/06/85
		US-A-	4577636	25/03/86
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		CA-A-	1244091	01/11/88