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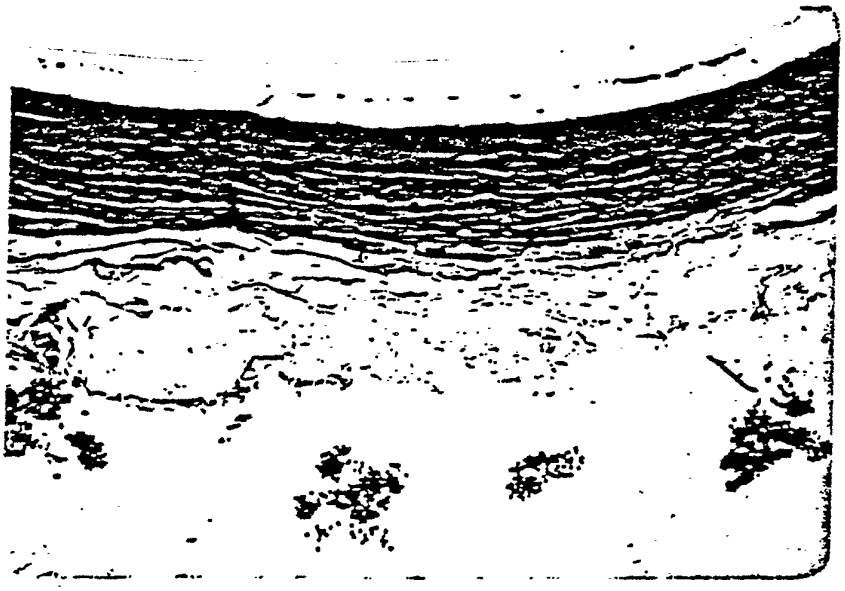
(54) Title: VASCULAR PROSTHESES



(57) Abstract

A vascular prosthesis is produced by subjecting a length of animal ureter to glutaraldehyde tanning. The lumen of the ureter is dilated and the ureter is set in the dilated configuration by the tanning process. The ureter may be strengthened by a surrounding sheath of polyester mesh. Ureters for use in the invention can be obtained from a wide range of animal species, but preferably from cattle and sheep. Prostheses can be produced in accordance with the invention for a wide range of revascularization surgery procedures in human patients.

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"VASCULAR PROSTHESES"

TECHNICAL FIELD

This invention relates to the field of surgery and more particularly to revascularization surgery.

As discussed in the specification of my copending Australian Patent Application No. 47208/79 (PD 4475) and corresponding U.S. Application Serial No. 041,620, the majority of deaths in the Western world are due to impaired arterial flow to distal tissues and revascularization surgery has become very common.

At the present time there are severe problems in obtaining suitable conduits for many revascularization procedures and it would be most desirable to have a bank of vascular prostheses, available in a range of diameters, which can give results comparable to autogenous saphenous vein grafts.

The aforesaid copending applications describe a vascular prosthesis comprised of a tube of collageous tissue which has been subjected to glutaraldehyde tanning and which is preferably reinforced with a tube of fibre mesh. Such a prosthesis can be obtained by implanting a rod or tube within a living host animal and allowing collageous tissue to form around the

implant. The implant and surrounding collageous tissue is subsequently removed and the collageous tissue then subjected to glutaraldehyde tanning.

I have now determined that animal ureters have adequate collagen content and luminal surface characteristics when subjected to glutaraldehyde tanning to perform satisfactorily as vascular grafts. This enables the preparation of vascular prostheses without the need for surgical procedures in host animals and it has been found that the resulting grafts can perform satisfactorily in wide ranging vascular situations. The ureters can be obtain from a wide range of animal species including humans, oxen, cows, sheep, goats, pigs, donkeys, camels, deer and kangaroos.

DISCLOSURE OF INVENTION

According to the invention there is provided a vascular prosthesis comprising a length of animal ureter which has been subjected to glutaraldehyde tanning. The invention also extends to the use of such a vascular prosthesis as a surgical graft in a living human patient.

The invention also provides a method of producing a vascular prosthesis for use as a surgical graft comprising subjecting a length of animal ureter to glutaraldehyde tanning.

Preferably, the ureter is encompassed by a fibre mesh sheath. Such sheath may, for example, be formed of a mesh woven from strands of multiple fine polyester fibres.

Preferably further, the wall of the lumen of the ureter is set in a dilated condition by the glutaraldehyde tanning so as to have a smooth, generally cylindrical surface.

BRIEF DESCRIPTION OF DRAWINGS

In the following detailed description of the preparation of vascular prostheses in accordance with the invention, reference will be made to the accompanying drawings in which;

Figure 1 is a reproduction of a photomicrograph showing a section through an ox ureter in its natural state;

Figure 2 is a reproduction of a photomicrograph showing a section through a vascular prosthesis produced in accordance with the invention; and

Figure 3 is a reproduction of a photomicrograph showing a section through a human saphenous vein.

BEST MODES OF CARRYING OUT THE INVENTION

In a typical preparation of vascular prostheses in accordance with the invention, ureters from human cadavers, oxen or other animals are obtained under abattoir conditions. They are transported to an aseptic area where they are cleaned of fat and adherent tissue. Glass rods of 2 mm to 10 mm diameter, depending on the size of the ureters, are inserted into the lumen of the ureters so that the ureters are supported on and stretched by the rods. More specifically, the rods are of such size as to dilate the lumen of the ureters so that thin walls become compressed into a close packed structure with a smooth generally cylindrical surface. This will be described more fully below with reference to Figures 1 and 2.

The lengths of the stretched ureters may vary from 10 cm to 60 cm according to the species of animal from which they are obtained. The glass rods and ureters are then covered with fine polyester mesh. This may be achieved by placing a tube of woven polyester mesh within a confining glass tube, then inserting the lumen on the glass rod through the mesh tube within the outer

glass tube, and finally withdrawing the glass rod, the ureter and the enveloping mesh together as a unit from the outer glass tube.

The polyester mesh covered ureters containing the glass rods of predetermined diameter and length are subjected to glutaraldehyde tanning by immersion in buffered glutaraldehyde. The buffered glutaraldehyde may have a glutaraldehyde strength in the range 0.05% to 10% and preferably about 2.5%. The buffer may be a phosphate such as Na_2HPO_4 or KH_2PO_4 or a carbonate buffer. The pH of the bath may be in the range 2 to 8 and is preferably about 7.4.

The ureter may be immersed in the buffered glutaraldehyde at room temperature for between 4 hours and 100 hours, preferably for about 72 hours.

After glutaraldehyde tanning the mesh covered ureter is bleached by immersion in a bath of hydrogen peroxide to remove all free glutaraldehyde. The bleaching bath may contain hydrogen peroxide in the range 1% to 10% and preferably about 5%.

After bleaching the ureter may be dialysed in sterile water. More particularly, it may be successively immersed in three separate water baths and kept stirred in each bath for about 3 hours.

After glutaraldehyde tanning, bleaching and dialysing, the ureteric grafts are individually packed in glass cylinders in 50% alcohol for preservation and storage.

When a ureteric graft produced in the above manner is to be prepared for implantation, it is removed from its individual glass storage cylinder and slid off the supporting glass rod. It is then soaked in three separate baths of heparinised saline (10,000 units per litre). Preferably, it is held in each bath for

about 20 minutes. It is then ready for surgical grafting.

In the accompanying drawings Figure 1 shows a section through an ox ureter in its natural state. It can be seen that the wall, although circular, is loosely packed and the central lumen is very constricted and of stellate formation. The darker areas in the ureter wall show the collagen content.

Figure 2 shows a section through a vascular prosthesis produced from an ox ureter in accordance with the invention. It can be seen that the lumen has been greatly dilated and the wall has been compressed to a compact structure having a smooth generally cylindrical surface, this structure being set by the glutaraldehyde tanning process. The bundles of dark spots appearing at the outside of the ureter are the strands of multiple fibres of the surrounding mesh sheath.

Figure 3 shows a section through a human saphenous vein. This exhibits a bumpy surface of bulges and crevices and a collagen density less than that in the prosthesis of Figure 2. The structure of prosthesis in Figure 2 is superior to that of the human saphenous vein which is being widely used in revascularization surgery with success.

Tanned ureteric vascular grafts prepared in the above manner have been evaluated in the following experimental procedures:

I ARTERIAL GRAFTS IN DOGS

Twelve adult mongrel dogs weighing 15 to 20 kg were anaesthetised and a mid-line laparotomy performed.

The first dog had a single bovine ureteric graft 10 cm long and 6 mm wide anastomised to the infrarenal aorta proximally and to the right common iliac artery distally. The terminal aorta was

ligated. The graft remained patent for 17 months documented by arteriograms and inspection on sacrifice. Histological examination did not show any biodegradation or luminal narrowing.

The subsequent 11 dogs had a bovine ureteric graft and an ovine biosynthetic graft of 10 cm long and 6 mm wide (in accordance with my aforesaid copending applications) inserted as parallel vascular grafts. Their proximal anastomoses were to infrarenal aorta. The distal anastomoses were to the right and left common iliac arteries. The terminal aorta was ligated. All animals had patent grafts up to two years as documented by periodic angiograms.

II SHUNTS IN PIGS

Nine anaesthetised four weeks old piglets weighing 7 to 10 kg were used to construct aorto-pulmonary shunts at left thoracotomy. The shunts were ovine ureteric grafts 6 mm wide and 3 cm long. Patency of the shunts of ureteric grafts were documented by haemodynamic measurements. All shunts were patent at four weeks. Similar shunts in piglets of same age and similar weight constructed with goretex and ovine biosynthetic grafts failed to maintain a shunt at four weeks.

III VENOUS SEGMENTAL REPLACEMENTS IN RABBITS

In ten anaesthetised adult rabbits a mid-line laparotomy was performed. After cross-clamping, a segment of infrarenal inferior venacava was excised and was replaced by 3 cm long and 3 mm wide ureteric grafts produced from pig ureters. All rabbits survived this procedure. None of them have shown any evidence of inferior venacaval obstruction. The first two rabbits were explored at one and two weeks post-operatively and showed widely patent grafts.

IV REVASCULARIZATION IN HUMAN PATIENTS

Four human patients have had limbs salvaged by lower limb revascularization using tanned bovine ureteric grafts produced in accordance with the invention. These patients still have viable limbs after periods ranging from three to six months from revascularization.

One patient has had two tanned bovine ureteric grafts implanted for myocardial revascularization with success. In both instances no conduit of apropriate size would have been available but for the present invention.

INDUSTRIAL APPLICABILITY

The above described results have established that animal ureters have adequate collageous content and luminal surface characteristics when subjected to glutaraldehyde processing in accordance with the invention and they can perform satisfactorily as vascular grafts. The experiment evaluation carried out for more than 2 years in 3 different species and in differing vascular situations has proved successful. The three differing situations of arterial, aorto-pulmonary shunts and segmental venous replacements imposed different types of stress on the ureteric grafts. In all cases the ureteric grafts performed successfully and consistently and their ability to remain patent in 3 mm diameters in a venous environment and their flexibility make them suitable for coronary grafts.

It has been found that bovine and ovine collagen have particularly desirable properties when subjected to glutaraldehyde tanning in accordance with the present invention. The reasons for this are not fully understood but grafts produced from cattle and sheep ureters have been most successful.

It is therefore anticipated that long grafts for limb salvage would normally be produced from ox ureters whereas smaller grafts would be produced from ureters taken from calves or sheep.

CLAIMS

1. A vascular prosthesis suitable for use as a surgical graft, characterized by a length of animal ureter which has been subjected to glutaraldehyde tanning.

2. A vascular prosthesis as claimed in claim 1, further characterized in that said length of animal ureter is encompassed by a fibre mesh sheath.

3. A vascular prosthesis as claimed in claim 2, further characterized in that said mesh is woven from strands of multiple fine polyester fibres.

4. A vascular prosthesis as claimed in any one of claims 1 to 3, further characterized in that the wall of the lumen of said ureter is set in a dilated condition by the glutaraldehyde tanning so as to have a smooth, generally cylindrical surface.

5. A vascular prosthesis as claimed in any one of claims 1 to 4, further characterized in that said ureter is an ovine ureter.

6. A vascular prosthesis as claimed in any one of claims 1 to 4, further characterized in that said ureter is a bovine ureter.

7. A method of producing a vascular prosthesis for use as a surgical graft characterized by the step of subjecting a length of animal ureter to glutaraldehyde tanning.

8. A method as claimed in claim 7, further characterized in that a rod or tube is inserted into the lumen of the animal ureter prior to glutaraldehyde tanning whereby to dilate the lumen wall such that it has a smooth generally cylindrically curved surface, the wall of the lumen is set in the dilated condition by the glutaraldehyde tanning, and the rod or tube is subsequently removed from the lumen.

9. A method as claimed in claim 8, further characterized in that a fibre mesh is applied about the length of animal ureter while it is supported on the rod or tube to form an external supporting sheath for the prosthesis.

10. A method as claimed in any one of claims 7 to 9, further characterized in that the animal ureter is an ovine ureter.

11. A method as claimed in any one of claims 7 to 9, further characterized in that the animal ureter is a bovine ureter.

12. A method as claimed in any one of claims 7 to 11, further characterized in that the length of ureter is tanned in buffered glutaraldehyde having a glutaraldehyde strength in the range 0.05% to 10%, preferably about 2.5%.

13. A method as claimed in claim 12, further characterized in that the buffered glutaraldehyde is maintained at a pH in the range 2 to 8, preferably about 7.4.

14. A method as claimed in claim 12 or claim 13, further characterized in that the length of ureter is immersed in the buffered glutaraldehyde for between 4 hours and 100 hours, preferably for about 72 hours.

15. A method of revascularization surgery, characterized in that a vascular prosthesis as claimed in any one of claims 1 to 6 is used as a surgical graft in a human patient.

16. A method of revascularization surgery, characterized in that a vascular prosthesis produced by the method claimed in any one of claims 7 to 14 is used as a surgical graft in a human patient.

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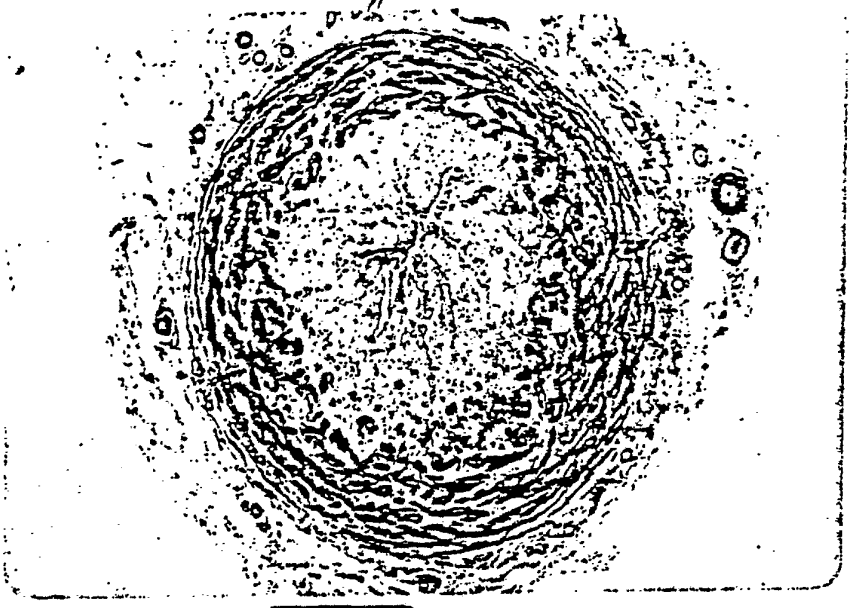

FIG. 1.

FIG. 2.

FIG. 3.

INTERNATIONAL SEARCH REPORT

International Application No PCT/AU 80/00080

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

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

Int.Cl.[3] A61F 1/00, C14C 3/16, A01N 1/00, B32B 1/08, 9/02

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC	A61F 1/00, 1/24

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

AU:IPC as above; Australian Classification 87.4, 47.2.

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	US, A, 3894530 published 1975, July 15, I.I. Dardik and H. Dardik	7,1
X	US, A, 3988782 published 1976, Nov. 2, I.I. Dardik and H. Dardik	7,1,8,12
X	US, A, 3974526 published 1976, Aug.17, I.I. Dardik and H. Dardik	7,1,2,9,13,14
X	CA, A, 1076752 published 1980, May 6,	7,1
A	DE, A, 2519107 published 1976, Jan. 15, W.D. Hancock, T.J. Fogarty	1,7,12
A	DE, A, 2519106 published 1976, Feb.5, W.D. Hancock, F.P. Sattler	7,1,12
X	AU, A, 47208/79, V. Ketharanathan, published 29 Nov. 1979	7,1,2,8,9, 12,13,14
A	W.C.McMaster, J. Kouzelos, S. Liddle, T.R. Waugh J. Biomed. Mater Res. 1976, 10(2)259-71 Tendon grafting with glutaraldehyde fixed material (see p.261 lines 1 and 2)	1,12,7,13

* Special categories of cited documents: [15]

"A" document defining the general state of the art

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IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
7 January 1981 (07.0181)	12 JANUARY 1981 (12.01.81)
International Searching Authority [1]	**Signature of Authorized Officer [20]**
Australian Patent Office	J.I.Welsh

Form PCT/ISA/210 (second sheet) (October 1977)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	H. Kambic, G. Picha, R. Kivaly, L. Koshino, Y. Nose Trans.Am.Soc. Artif. Intern.Organs.1976, 22, 664-72 Application of aldehyde treatments to cardiovascular devices (see p.665 lines 6 and 7)	7,1,12,13,14

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

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:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

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:

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.