An implantable bioartificial pancreas device having an islet chamber containing glucose responsive and insulin-secreting islets of Langerhans or similar hormone secreting cells, the islet chamber having baffle means inside thereof to assist in even distribution of the islets in the chamber, one or more vascularizing chambers open to surrounding tissue, a semi-permeable membrane between the islet and vascularizing chambers that allows passage of small molecules including insulin, oxygen and glucose and does not allow passage of agents of the immune system such as white cells and antibodies, the vascularizing chambers containing a growth factor soaked fibrous or foam matrix having a porosity of about 40 to 95%, the matrix providing small capillary growth and preventing the blood from clotting in the lower chamber.
This application is a continuation-in-part application of Ser. No. 07/922,562 filed Jul. 30, 1992 now abandoned.

FIELD OF THE INVENTION

The present invention is directed to a bioartificial implantable pancreas for the treatment of insulin dependent diabetes mellitus.

BACKGROUND OF THE INVENTION

There is a need to provide a biocompatible and implantable device containing islets of Langerhans, or the beta cells thereof, that can supply the hormone insulin for the purpose of controlling blood glucose levels in people with diabetes mellitus requiring insulin. Insufficient regulation of blood glucose levels in people with diabetes has been associated with the development of long-term health problems such as kidney disease, blindness, coronary artery disease, stroke, and gangrene resulting in amputation. Therefore, there is a need to replace conventional insulin injections with a device that can provide more precise control of blood glucose levels. An implantable bioartificial pancreas device which was evaluated in dogs by Monaco et al. was recently described in the following articles: “Successful treatment of diabetes with the biohybrid artificial pancreas in dogs” Transplantation 51, 43–51, January, 1991; “Biohybrid artificial pancreas: Long-term implantation studies in diabetic, pancreatectomized dogs” Science 252, 718–721, May 1991; “Transplantation of islet allografts and xenografts in totally pancreatectomized diabetic dogs using the hybrid artificial pancreas” Ann. Surg. 214 339–362 September, 1991. The device described in these articles was a chamber containing a coiled copolymer tubular membrane which transferred the blood flow. The coiled copolymer tubular membrane had a nominal porosity of 80,000 daltons which permit free passage of nutrients and insulin but inhibit passage of the agents of the immune system (immunoisolation). Surrounding the outside of the coiled tubular membrane and within the chamber were placed islets of Langerhans. The islets of Langerhans are composed primarily of α, β, δ and PP cells which synthesize and secrete the hormones glucagon, insulin, somatostatin, and pancreatic polypeptide respectively.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide an easily implantable, easily used bioartificial pancreas device which provides a site-specific natural, nonclotting blood supply to immunoprotected islets of Langerhans and minimizes fibrotic overgrowth and encapsulation.

It is another object of the invention to provide the above described device with an upper chamber containing the islets of Langerhans (islet chamber) or other secreting cells such as neurons, pituitary, parathyroid, liver, adrenal and ovarian and a means for adding and removing them via an inlet and outlet catheter with ports, and a lower chamber (vascularizing chamber) containing a fibrous or sponge-like matrix having a porosity of about 40 to 90 percent, the matrix having an
angiogenic stimulating growth factor such as heparin
binding growth factor, collagen, endothelial cell
growth factor, acidic and basic fibroblast growth factor
material and porous openings with average pore size in
the range of 10 to 200 microns to facilitate the growth of
the neovessels. The matrix material containing the
growth factor stimulates the surrounding tissue of the
host to penetrate the matrix and vascularize it much like
the process of wound healing, with the result that the
device develops its own blood supply after a sufficient
period of time, usually within four weeks. The device
includes a semipermeable membrane made of any natu­
ral or synthetic material providing a molecular weight
cut-off of less than 100,000 that is placed between the
upper (islet) and lower (vascularizing) chambers to
protect the islets of Langerhans from the agents of the
host's immune system (immunoisolation) while allow­
ing passage of smaller nutrient molecules such as glu­
cose and oxygen as well as insulin. An extension of this
description would include placement of the islets of
Langerhans in a central islet chamber which, in one
embodiment, is sandwiched between two outer vascular­
izing chambers containing the growth factor and ma­
trix material, with a means of adding or removing the
islets. Semipermeable membranes for immunoprotec­
tion of the islets would separate the islets in the central
chamber from the outer chambers. Each outer chamber
containing the growth factor and matrix would have
the same characteristics and functions described above.

It is an object of the present invention to provide a
method of using the above bioartificial pancreas device,
the method including:
a) providing the bioartificial pancreas as described in the preceding objects;
b) making the thickness of the pancreas about 1 to 10
millimeters, its diameter depending on the size,
weight, and age of the patient as well as the number
of islets needed for effective treatment;
c) implanting the pancreas in a mammal; and
d) immunoisolating the implanted islets of Langer­
hans.

The method also includes:
e) using islet of Langerhans or the beta cells there­
from obtained from a human pancreas or animal
sources such as the pig, cow, dog, or rat or insulin
secreting cells either naturally occurring or experi­
mentally derived; and
f) a porous support matrix using angiogenic growth
factors to stimulate device vascularization which
minimizes fibrotic overgrowth and encapsulation.

DESCRIPTION OF THE DRAWINGS

These and other objects will be apparent from the
specification that follows, the appended claims, and the 55
drawings in which:

FIG. 1 is a perspective view of an implantable bioar­
tificial pancreas;
FIG. 2 is a perspective view of another implantable
pancreas having dual matrix layers;
FIG. 3 is a sectional view of the bioartificial pancreas
of FIG. 1; and
FIG. 4 is a sectional view of the pancreas of FIG. 2.
FIG. 5a is a top plan view of the first chamber show­
ing baffle means for assisting in even distribution of
biologically active cells such as islets of Langerhans;
FIG. 5b is another embodiment showing baffle means
in the first chamber;

FIG. 5c is still another embodiment showing baffle
means in the first chamber;
FIG. 6 is a perspective view of a first chamber for
islets and other active cells, the chamber being in the
form of an elongated tube or hollow fiber;
FIG. 6a is a side elevational view of another embody­
ment showing the first chamber in the form of a heli­
cally shaped hollow fiber; and
FIG. 7 is a top plan schematic view of a plurality of
first chamber hollow fibers, the follow fibers being a
common inlet and a common outlet.

SUMMARY OF THE INVENTION

The present invention provides an implantable bioar­
tificial pancreas comprising a device having an enclosed
islet chamber and one or more vascularizing chambers
having an opening at one end thereof that provides
access to surrounding tissue, a plurality of insulin­
secreting islets of Langerhans in the islet chamber, inlet
means for supplying islets to the islet chamber, outlet
means for removing islets from the islet chamber, a
semi-permeable membrane(s) between the islet and vas­
cularizing chambers, the membrane(s) providing a mo­
lecular weight cut-off less than about 100,000 thereby
immunoprotecting the islets from the vascular area
within the vascularizing chamber and around the im­
planted vascularizing chamber, the membrane(s) allow­
ing passage of molecules with molecular weights less
than 100,000, including glucose, oxygen and insulin
between the islet and vascularizing chambers and not
allowing passage of agents of the immune system such as
leukocytes, antibodies, and complement to the islet
chamber, and a biocompatible fibrous or porous foam
matrix in the vascularizing chamber to provide a neo­
vascular formation region for enhancing the growth of
small capillaries for providing efficient mass transfer of
nutrients and insulin between the islet chamber and the
blood stream in the vascularizing chamber, the fibrous
or foam matrix having a porosity of about 40 to 95
percent and interconnecting passageways that are
equivalent to an open-celled foam having an average
core size of about 10 to 200 microns, the fibers and foam
being of an organic or inorganic material, the organic
material composed principally of carbon, oxygen, and
hydrogen atoms and optionally, nitrogen and sulfur
atoms, the inorganic materials being composed of one
or more of carbon, titanium, silica, sodium, calcium,
strontium, magnesium, zinc and boron atoms.

The present invention also provides a method of
presenting insulin-secreting islets of Langerhans to the
vascular system of a mammal, the method comprising:
A. providing a bioartificial pancreas as defined above;
B. making the thickness of the pancreas about 1 to 10
millimeters; and
C. implanting the pancreas in a mammal such as in the
peritoneal cavity which presents the insulin di­
rectly to the liver which is known to be more effec­
tive.

DETAILS OF THE INVENTION

As seen in the drawings, FIG. 1 and 3, a bioartificial
pancreas device 1 comprises an islet-containing upper
chamber 5, an open on one end vascularizing lower
chamber 10, and inlet and outlet means 15 for supplying
islets of Langerhans 20 to the islet containing chamber.
A semi-permeable membrane 25 is provided between
the islet and vascularizing chambers. The membrane 25
allows passage of nutrients and small vital molecules.
silicones, organopolysiloxanes and graphite and combi-
absorbable by the body of the mammal and minimizes
being about 10 to 30 microns.

The matrix 30 generally has a porosity of as low as
about 40 to 50 percent and as high as about 90 to 95%
percent. The matrix porosity is preferably about 80 to
90 percent. The matrix foam is an open-celled structure
and generally has an average pore size of about 10 to
200 microns, the preferred size being about 50 to 100
microns.

Although the islets of Langerhans cells are highly
preferred, other cellular transplants can be used that
require immunoprotection and that secrete or metabo-
lize a substance that can permeate the membrane 25.
The secreted substances may, for example, be from
liver, parathyroid, thyroid, pituitary, neural, adrenal,
ovarian or genetically engineered cells. Other useful
cells may perform detoxifying functions by removing
and metabolizing toxic substances found in the blood-
stream.

The fibrous matrix has interconnected openings
equivalent in porosity and size openings that are ap-
proximately equivalent to the size openings to the foam
matrix just described. Hence, the fiber openings are
equivalent to the 10 to 200 microns set forth for the
foam. The fibers are generally about 10 to 60 or 100
microns in diameter, the preferred average diameter
being about 10 to 30 microns.

The total thickness of the matrix is about 1 to 4 mm,
the preferred thickness being about 2 to 3 mm. The
matrix thickness, thus, is sufficient to absorb proteins,
ECM materials, growth factor materials, develop a
blood supply, and the matrix also is preferably non-
absorbable by the body of the mammal and minimizes
fibrotic overgrowth and encapsulation.

Suitable matrix materials are keratin (silk, wool, hair),
collagen, of various types, polyolefins such as polyeth-
ylene, polypropylene and polybutylene, polyesters such
as polyethylene terephthalate and polyethylene adipate,
polyurethanes such as polyesterurethanes and polyethe-
rurethanes, glass including glass fibers, stainless steel,
silicones, organopolysiloxanes and graphite and combi-
nations thereof. The keratin matrix is keratin, keratin-
containing or keratin-like.

The pore size of the highly preferred matrix is at least
about 10 microns and optimally 50 to 100 or 120
microns.

For some applications, suitable matrix materials are
polyamides including nylon such as polycaprolactam
and polyhexamethylene adipate, polyamide-imides,
polyamides including nylon such as polycaprolactam,
polycarbonates, polyacrylates including polymethyl
methacrylate and polyethylmethacrylate and polysul-
phene.

A suitable fiber and foam matrix is organic or inor-
ganic, the organic material being composed principally
of carbon, oxygen, and hydrogen atoms, and optionally
nitrogen and/or sulfur atoms. Organic material such as
polyolefins, composed of carbon and oxygen atoms are
highly useful, such hydrocarbon polymers being non-
halogenated and non-fluorinated.

Excellent results have been obtained when the matrix
is made of hair in which the average diameter of the hair
fiber is about 10 to 15 microns, the fiber length is about
½ to 2 inches, the matrix thickness is about 2 to 3 milli-
meters and the porosity is about 80 to 85 percent.

In operation after implantation in the peritoneal cavity,
or other suitable site, and after a sufficient period of
time for device vascularization, usually about four
weeks, the islets of Langerhans are delivered to the
device islet chamber via the inlet and outlet catheters
and ports. The islets take up residence within the islet
chamber of the device and are provided with essential
nutrients and oxygen via mass transfer from across the
immunoprotective membrane from the vascularized
chamber of the device. For example, as blood glucose
levels rise following a meal, the glucose levels rise rap-
Idly within the vascularized region of the device and


system including growth of small capillaries.

FIG. 7 shows a plan view of four hollow fiber 70/ma-
trix 80 first chamber assemblies. The first chambers 85
are connected together with a common inlet 90 and a
common outlet 91.

In the embodiments shown in FIGS. 5c, 5b, 5c, 6, 6a
and 7, the active cells such as the islets form a layer next
to a semi-permeable membrane 95 such as the mem-
brane 25 in FIGS. 3 and 4. The baffie means provides an
even distribution of the active cells as they are introduced into the first chamber and used therein.

Thus, the present invention provides an effective and highly useful bioartificial organ for implantation into an animal comprising a housing having a first enclosed chamber containing metabolically active cells, at least one vascularizing chamber having an opening on one end thereof that provides access to surrounding tissue, inlet means for supplying cells to the first chamber, outlet means for removing cells from the first chamber, and a semi-permeable membrane separating and in communication with the first chamber and vascularizing chamber, the membrane providing immunoprotection of the active cells from the vascular area within the vascularizing chamber and around the implanted device, the membrane allowing passage of small molecules including nutrients and waste products between the first and vascularizing chambers and not allowing passage of agents of an immune system to the first chamber, and a biocompatible fibrous or porous foam matrix in the vascularizing chamber to provide a neovascular formation region for enhancing growth of small capillaries for providing efficient mass transfer of substances between first chamber and the capillaries in the vascularizing chamber, the fibrous or foam matrix having a porosity of about 40 to 95 percent and interconnecting passageways of about 10 to 120 microns, the fibers and foam being of an organic or inorganic material, the organic material composed principally of carbon, oxygen, and hydrogen atoms and optionally, nitrogen and sulfur atoms, the inorganic materials being composed of one or more of carbon, titanium, silica, sodium, calcium, strontium, magnesium, zinc and boron atoms, there being baffle means in the first enclosed chamber for assisting in even distribution of the metabolically active cells.

What is claimed is:

1. A bioartificial organ for implantation into an animal comprising a housing having a first enclosed chamber containing metabolically active cells, at least one vascularizing chamber having an opening on one end thereof that provides access to surrounding tissue, inlet means for supplying cells to the first chamber, outlet means for removing cells from the first chamber, and a semi-permeable membrane separating and in communication with the first chamber and vascularizing chamber, the membrane providing immunoprotection of the active cells from the vascular area within the vascularizing chamber and around the implanted device, the membrane allowing passage of small molecules including nutrients and waste products between the first and vascularizing chambers and not allowing passage of agents of an immune system to the first chamber, and a biocompatible fibrous or porous foam matrix having fibers or foam in the vascularizing chamber to provide a neovascular formation region for enhancing growth of small capillaries for providing efficient mass transfer of substances between first chamber and the capillaries in the vascularizing chamber, the fibrous or foam matrix having a porosity of about 40 to 95 percent and interconnecting passageways having an average pore size of about 10 to 200 microns, the fibers and foam being of an organic or inorganic material, the organic material composed principally of carbon, oxygen, and hydrogen atoms and optionally, nitrogen and sulfur atoms, the inorganic materials being composed of at least one of carbon, titanium, silica, sodium, calcium, strontium, magnesium, zinc and boron atoms, and there being baffle means inside the first chamber to assist in even distribution of the metabolically active cells within the islet area.

2. A bioartificial organ as defined in claim 1 in which the baffle means is a baffle plate in the first chamber.

3. A bioartificial organ as defined in claim 1 in which the baffle means is three baffle plates generally parallel to each other to provide even distribution of the cells in the first chamber.

4. An organ as defined in claim 3 in which there are three baffle plates.

5. A bioartificial organ as defined in claim 1 in which the baffle means is spiral-shaped coil forming a labyrinth inside the first chamber to assist in even distribution of the cells.

6. A bioartificial implantable pancreas comprising a housing having a first enclosed chamber containing islets of Langerhans, at least one vascularizing chamber having an opening on one end thereof that provides access to surrounding tissue, a plurality of insulin-secreting islets of Langerhans in the first chamber, inlet means for supplying islets to the first chamber, outlet means for removing islets from the first chamber, a semi-permeable membrane between the first islet chamber and vascularizing chamber, the membrane providing immunoprotection of the islets from the vascular area within the vascularizing chamber and around the implanted device, the membrane allowing passage of small molecules including oxygen and insulin between the first and vascularizing chambers and not allowing passage of agents of the immune system to the first chamber, and a biocompatible fibrous or porous foam matrix having fibers or foam in the vascularizing chamber to provide a neovascular formation region for enhancing the growth of small capillaries for providing efficient mass transfer of nutrients, glucose, oxygen, and insulin between in the islet chamber and the blood stream in the vascularizing chamber, the fibrous or foam matrix having a porosity of about 40 to 95 percent and interconnecting passageways having an average pore size of about 10 to 200 microns, the fibers and foam being of an organic or inorganic material, the organic material composed principally of carbon, oxygen, and hydrogen atoms and optionally, nitrogen and sulfur atoms, the inorganic materials being composed of at least one of carbon, titanium, silica, sodium, calcium, strontium, magnesium, zinc and boron atoms, and there being baffle means inside the first chamber to assist in providing an even distribution of the islet cells in the first chamber.

7. A bioartificial organ for implantation into an animal comprising a housing having a first enclosed chamber containing metabolically active cells, at least one vascularizing chamber having an opening on one end thereof that provides access to surrounding tissue, inlet means for supplying cells to the first chamber, outlet means for removing cells from the first chamber, and a semi-permeable membrane separating and in communication with the first chamber and vascularizing chamber, the membrane providing immunoprotection of the active cells from the vascular area within the vascularizing chamber and around the implanted device, the membrane allowing passage of small molecules including nutrients and waste products between the first and vascularizing chambers and not allowing passage of agents of an immune system to the first chamber, and a biocompatible fibrous or porous foam matrix having
fibers and foam in the vascularizing chamber to provide a neovascular formation region for enhancing growth of small capillaries for providing efficient mass transfer of substances between first chamber and the capillaries in the vascularizing chamber, the fibrous or foam matrix having a porosity of about 40 to 95 percent and interconnecting passageways of about 10 to 120 microns, the fibers and foam being of an organic or inorganic material, the organic material composed principally of carbon, oxygen, and hydrogen atoms and optionally, nitrogen and sulfur atoms, the inorganic materials being composed of at least one of carbon, titanium, silica, sodium, calcium, strontium, magnesium, zinc and boron atoms, the first active cell containing chamber being a longitudinally extending hollow fiber.

8. An organ as defined in claim 7 in which cell containing chamber is coiled helically-shaped hollow fiber.

9. An organ as defined in claim 7 in which there are a plurality of parallel hollow fibers, each inlet means and outlet means of the fibers being connected to a common feed source and a common exit source.